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(54) Title: TREATMENT OF SEPTIC SHOCK WITH CONJUGATED BIOLOGICALLY ACTIVE PEPTIDES

(57) Abstract

A compound which is a conjugate of a biologically active amphiphilic peptide and a conjugate moiety. The conjugate moiety may be a carbohydrate (such as dextran or hetastarch); a protein; polyvinyl pyrrolidone; a polyalkylene glycol; or polyvinyl alcohol. Such compounds neutralize bacterial endotoxins, and thus are particularly useful in the treatment or prevention of septic shock.

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TREATMENT OF SEPTIC SHOCK WITH CONJUGATED BIOLOGICALLY ACTIVE PEPTIDES

This invention relates to the treatment of septic shock. More particularly, this invention relates to the treatment of septic shock by administering biologically active peptides including conjugate moieties.

Septic shock is a type of shock associated with overwhelming infection. Most commonly, the infection is produced by Gram-negative bacteria (such as, for example, E.coli, Pseudomonas species, and Bacteroides species), although other bacteria, viruses, fungi, and protozoa may also be causes. The shock is believed to be caused by the action of endotoxins (such as the liposaccharide or LPS in bacterial cell walls), other products of the infectious agent, or host mediators released in response to the infectious agent or the vascular system. Such action causes altered patterns of perfusion of tissues and large volumes of blood to be sequestered in the capillaries and veins. Bacterial endotoxin, such as LPS, at concentrations as low as a few micrograms per liter can activate immune cells in vitro. The majority of damage induced from the presence of LPS is not due to the LPS itself, but is a result of the body's complex reaction to the foreign LPS. This response

is mediated by immune cell activation and the resultant damage that these activated cells cause to the host tissues.

Septic shock or septicemia is difficult to reverse. Treatment following the initial signs of septic shock includes the infusion of normal saline or lactated Ringer's solution. If the shock persists, then an aggressive fluid challenge may be started, and the use of dopamine and/or norepinephrine may be recommended. More recent approaches to the treatment of septic shock are directed to the killing of bacteria and neutralizing LPS endotoxin with specific monoclonal antibodies; human bacteria permeability increasing protein (BPI); endotoxin neutralizing protein (ENP, which is obtained from the horseshoe crab); or synthetic molecules.

European Patent Application No. 428,486 discloses a conjugate of polymyxin B and a carrier, which may be employed in neutralizing bacterial endotoxins. The carrier may be a polysaccharide such as dextran or hydroxyethyl starch; a protein such as albumin; polyvinylpyrrolidone; polyethylene glycol; or polyvinyl alcohol.

In accordance with an aspect of the present invention, there is provided a compound which is a conjugate of: (i) a biologically active amphiphilic peptide, said peptide being an ion channel-forming peptide; and (ii) a conjugate moiety selected from the group consisting of: (a) carbohydrates; (b) proteins; (c) polyvinylpyrrolidone; (d) polyalkylene glycols; and (e) polyvinyl alcohol.

The compounds of the present invention are particularly applicable to the treatment of septic shock in that such compounds neutralize bacterial endotoxins. In general, the peptides are positively charged, while in general, the bacterial endotoxins are negatively charged. The compounds are particularly useful in that such compounds neutralize bacterial endotoxins without neutralizing essential proteins

in plasma (such as heparin, for example). In addition the compounds can be constructed such that they have a longer duration of activity than unconjugated peptides.

The conjugate moiety may be attached to the peptide at the C-terminal, at the N-terminal, or to an internal amino acid residue. It is to be noted, however, that the conjugate moiety should be attached to the peptide such that the peptide retains its positive charge.

In one embodiment, the conjugate moiety is a carbohydrate. Carbohydrates which may be conjugated to the peptide include, but are not limited to, dextran, hetastarch, hydroxyethyl starch, cellobiose, lactobiose, mannobiose, melibiose, lactobionic acid, and glucosamine. In one embodiment, the carbohydrate is dextran. In another embodiment, the carbohydrate is hetastarch.

Such carbohydrates may be conjugated to the peptide at the C-terminal, the N-terminal, or to an internal amino acid. The carbohydrate may be attached through a carbamate linkage, through an amine linkage, through an ester linkage, or through bifunctional crosslinking agents.

Ester linkages of the peptide with the carbohydrate may be formed by reacting the peptide and the carbohydrate in the presence of EDCI and DMAP. The C-terminus of the peptide reacts with an -OH group of the carbohydrate to form an ester bond.

Amine linkages may be formed by oxidizing the carbohydrate with periodate to form aldehyde groups. The aldehyde is then reacted with an amino group on the peptide to form a Schiff base which then can be reduced to an amine.

If the reaction with the carbohydrate aldehyde is with hydroxylamine instead of the peptide, followed by reduction, the product is an amino-carbohydrate. The amino-carbohydrate can be reacted with a peptide to form an amide linkage.

Carbamate linkages may be formed by treating the carbohydrate with 1-cyano-4-dimethyl-amino pyridinium tetrafluoroborate (CDAP), and then reacting the treated carbohydrate with a peptide having a free amino group to form a carbamate linkage.

Bifunctional crosslinking agents which may be employed for attacking the carbohydrate to the peptide include, but are not limited to, malimido groups, - S - S - O groups, and groups. Such groups may be attached to the carbohydrate first by attaching a -COOH group to the functional group, and then reacting the modified functional group with an -OH group of the carbohydrate to provide a carbohydrate containing the functional group. The carbohydrate with the functional group attached is then reacted with an -SH group attached to a peptide to form the conjugate.

Proteins which may be conjugated to the peptide include, but are not limited to, albumin, α_2-macroglobulin, antibodies or other proteins found in plasma. The peptide may be coupled to the protein via disulfide, amide, ester, ether, or other forms of covalent bonds.

Polyvinyl pyrrolidone may be attached to the peptide through ester linkages, through carbamate linkages, or through bifunctional crosslinking agents, such as those hereinabove described.

Polyalkylene glycols which may be conjugated to the peptide include, but are not limited to, polyethylene glycol.

The polyalkylene glycol may be attached to the peptide through ester linkages, carbamate linkages, or through bifunctional crosslinking agents, whereby free -OH groups of the polyalkylene glycol are reacted to form such linkages.

The polyvinyl alcohol also may be attached to the peptide through the linkages hereinabove described.

The biologically active amphiphilic peptides employed in the present invention are generally water-soluble to a concentration of at least 20 mg/ml at neutral pH in water. In addition, the structure of such peptide provides for flexibility of the peptide molecule. Such peptides are capable of forming an alpha-helix. When the peptide is placed in water, it does not assume an amphiphilic structure. When the peptide encounters an oily surface or membrane, the peptide chain folds upon itself into a rod-like structure.

In general, such peptides have at least 7 amino acids. In most cases, such peptides do not have in excess of 50 amino acids.

In general, the biologically active peptides are ion channel-forming peptides. An ion channel-forming peptide or ionophore is a peptide which increases the permeability for ions across a natural or synthetic lipid membrane. B. Christensen, et al., PNAS, Vol. 85, pgs. 5072-76 (July 1988) describe methodology which indicates whether or not a peptide has ion channel-forming properties and is therefore an ionophore. As used herein, an ion channel-forming peptide is a peptide which has ion channel-forming properties as determined by the method of Christensen, et al.

An amphiphilic peptide is a peptide which includes both hydrophobic and hydrophilic peptide regions.

The compounds may be administered in an amount effective to treat or prevent septic shock in a host. Preferably, the compounds are administered in an amount of from about 1 µg/kg to about 5 mg/kg per host weight. The compounds may be administered to a host in vivo, such as,

for example, through systemic administration, such as intravenous or intraperitoneal administration.

The compounds are administered in combination with an acceptable pharmaceutical carrier or vehicle such as a filler, non-toxic buffer, or physiological saline solution. The compounds may also be used in combination with adjuvants, protease inhibitors, or compatible drugs.

In one embodiment, the peptide is a basic (positively charged) polypeptide having at least sixteen amino acids wherein the polypeptide includes at least eight hydrophobic amino acids and at least eight hydrophilic amino acids. Still more particularly, the hydrophobic amino acids are in groups of two adjacent amino acids, and each group of two hydrophobic amino acids is spaced from another group of two hydrophobic amino acids by at least one amino acid other than a hydrophobic amino acid (preferably at least two amino acids) and generally by no greater than four amino acids, and the amino acids between pairs of hydrophobic amino acids may or may not be hydrophilic.

The hydrophilic amino acids are generally also in groups of two adjacent amino acids in which at least one of the two amino acids is a basic hydrophilic amino acid, with such groups of two hydrophilic amino acids being spaced from each other by at least one amino acid other than a hydrophilic amino acid (preferably at least two amino acids) and generally no greater than four amino acids, and the amino acids between pairs of hydrophilic amino acids may or may not be hydrophobic.

In accordance with a particularly preferred embodiment, the polypeptide comprises a chain of at least four groups of amino acids, with each group consisting of four amino acids. Two of the four amino acids in each group are hydrophobic amino acids, and two of the four amino acids in each group are hydrophilic, with at least one of the hydrophilic amino

acids in each group being a basic hydrophilic amino acid and the other being a basic or neutral hydrophilic amino acid.

The hydrophobic amino acids may be selected from the class consisting of Ala, Cys, Phe, Gly, Ile, Leu, Met, Pro, Val, Trp, Tyr, norleucine (Nle), norvaline (Nva), and cyclohexylalanine (Cha). The neutral hydrophilic amino acids may be selected from the class consisting of Asn, Gln, Ser, Thr and homoserine (Hse). The basic hydrophilic amino acids may be selected from the class consisting of Lys, Arg, His, Orn, homoarginine (Har), 2, 4-diaminobutyric acid (Dbu), and p-aminophenylalanine.

Each of the groups of four amino acids may be of the sequence ABCD, BCDA, CDAB, or DABC, wherein A and B are each hydrophobic amino acids and may be the same or different, one of C or D is a basic hydrophilic amino acid, and the other of C or D is a basic or neutral hydrophilic amino acid and may be the same or different. In one embodiment, the polypeptide chain may comprise 5 or 6 groups of this sequence. In each group, each of A, B, C and D may be the same in some or all of the groups or may be different in some or all of the groups.

The polypeptide chain preferably has at least 20 amino acids, and no greater than 50 amino acids. It is to be understood, however, that the polypeptide does not have to consist entirely of the groups described above. The polypeptide may have amino acids extending from either or both ends of the noted groups forming the polypeptide chain and/or there may be amino acids between one or more of the at least four groups and still remain within the scope of the invention.

The groups of amino acids may be repeating groups of amino acids, or the amino acids in the various groups may vary provided that in each group of the at least four groups

of amino acids there are two hydrophobic and two hydrophilic amino acids as hereinabove noted.

Thus the biologically active polypeptide may comprise a chain including at least four groups of amino acids, each containing four amino acids. Two of the four amino acids in each group are hydrophobic, at least one amino acid is basic hydrophilic, and the remaining one is basic or neutral hydrophilic, with the polypeptide chain preferably having at least 20 amino acids but no greater than 50 amino acids.

In one embodiment, each of the at least four groups of amino acids which are in the peptide chain is of the sequence A-B-C-D, B-C-D-A, C-D-A-B or D-A-B-C wherein A and B are hydrophobic amino acids, one of C or D is a basic hydrophilic amino acid, and the other of C or D is basic or neutral hydrophilic amino acid. The resulting polypeptide chain, therefore, may have one of the following sequences:

$(X_1)_a(A\text{-}B\text{-}C\text{-}D)_n(Y_1)_b$

$(X_2)_a(B\text{-}C\text{-}D\text{-}A)_n(Y_2)_b$

$(X_3)_a(C\text{-}D\text{-}A\text{-}B)_n(Y_3)_b$

$(X_4)_a(D\text{-}A\text{-}B\text{-}C)_n(Y_4)_b$

wherein X_1 is D; C-D- or B-C-D-, Y_1 is -A or -A-B or -A-B-C

X_2 is A-, D-A- or C-D-A-

Y_2 is -B, -B-C or B-C-D

$X_3$is B-, A-B-, D-A-B-

Y_3 is -C, -C-D, -C-D-A

$X_4$is C-, B-C-, A-B-C-

Y_4 is -D, -D-A, -D-A-B

a is 0 or 1; b is 0 or 1

and n is at least 4.

It is to be understood that the peptide chain may include amino acids between the hereinabove noted groups of four amino acids provided that the spacing between such groups and the charge on the amino acids does not change the characteristics of the peptide chain which provide

amphiphilicity and a positive charge and do not adversely affect the folding characteristics of the chain to that which is significantly different from one in which the hereinabove noted group of four amino acids are not spaced from each other.

As representative examples of such peptides, there may be mentioned.

I Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys (SEQ ID NO:1)

II Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys. (SEQ ID NO:2)

III Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala- (SEQ ID NO:3)

IV Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe- (SEQ ID NO:4)

V Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser-Lys-Ala-Phe-Ser (SEQ ID NO:5)

The peptide may have amino acids extending from either end of the chain. For example, the chains may have a Ser-Lys sequence before the "Ala" end, and/or an Ala-Phe sequence after the "Lys" end. Other amino acid sequences may also be attached to the "Ala" and/or the "Lys" end.

Similarly, in any polypeptide chain having at least four groups of amino acids of the sequence as described above, the chain may have, for example, a C-D sequence before the first A-B-C-D group. Also other amino acid sequences may be attached to the "A" and/or the "D" end of one of these polypeptide chains. Also there may be amino acids in the chain which space one or more groups of the hereinabove noted four amino acids from each other.

In accordance with another embodiment, the peptide may be a magainin peptide.

A magainin peptide is either a magainin such as magainin I, II or III or an analogue or derivative thereof. The magainin peptides preferably include the following basic peptide structure X_{12}:

-- R_{11}-R_{11}-R_{12}-R_{13}-R_{11}-R_{14}-R_{12}-R_{11}-
R_{14}-R_{12}-R_{11}-R_{11}-R_{11}-R_{14a}-$(R_{15})_n$-R_{14a}-R_{14} --

wherein R_{11} is a hydrophobic amino acid, R_{12} is a basic hydrophilic amino acid; R_{13} is a hydrophobic, neutral hydrophilic, or basic hydrophilic amino acid; R_{14} and R_{14a} are hydrophobic or basic hydrophilic amino acids; R_{15} is glutamic acid or aspartic acid, or a hydrophobic or a basic hydrophilic amino acid, and n is 0 or 1. In a preferred embodiment, R_{13} is a hydrophobic or neutral hydrophilic amino acid, R_{14a} is a hydrophobic amino acid, and R_{15} is glutamic acid or aspartic acid.

Thus, for example, a magainin peptide may include the following structure:

-Y_{12}-X_{12}-

where X_{12} is the hereinabove described basic peptide structure and Y_{12} is

(i) R_{12}

(ii) R_{14a}-R_{12}

(iii) R_{11}-R_{14a}-R_{12}

(iv) R_{14}-R_{11}-R_{14a}-R_{12}

where R_{11}, R_{12}, R_{14} and R_{14a} are as previously defined.

A magainin peptide may also have the following structure:

-X_{12}-Z_{12}-

wherein X_{12} is as previously defined and Z_{12} is:

(i) R_{16} where R_{16} is a basic hydrophilic amino acid or asparagine or glutamine.

(ii) R_{16}-R_{17} where R_{17} is a neutral hydrophilic amino acid, a hydrophobic amino acid, or a basic hydrophilic amino acid. Preferably, R_{17} is a neutral hydrophilic amino acid.

A magainin peptide may also have the following structure:

$$(Y_{12})_a\text{-}X_{12}\text{-}(Z_{12})_b$$

where X_{12}, Y_{12} and Z_{12} are as previously defined and a is 0 or 1 and b is 0 or 1.

The magainin peptides may also include the following basic peptide structure X_{13}:

--R_{14}-R_{11}-R_{14a}-R_{12}-R_{11}-R_{11}-R_{12}-R_{13}-
R_{11}-R_{14}-R_{12}-R_{11}-R_{11}-R_{12}-, wherein R_{11}, R_{12}, R_{13}, R_{14}, and R_{14a} are amino acids as hereinabove described.

The magainin peptide may also include the following structure X_{13}-Z_{13}; wherein X_{13} is the hereinabove described basic peptide structure and Z_{13} is $(R_{11})_n$-$(R_{11})_n$-$(R_{11})_n$-$(R_{14a})_n$-$(R_{15})_n$-$(R_{14a})_n$-$(R_{14})_n$--$(R_{16})_n$-$(R_{17})_n$ wherein R_{11}, R_{14}, R_{14a}, R_{15}, R_{16}, and R_{17} are as hereinabove described, and n is 0 or 1, and each n may be the same or different.

The magainin peptides generally include at least fourteen amino acids and may include up to forty amino acids. A magainin peptide preferably has 22 or 23 amino acids. Accordingly, the hereinabove described basic peptide structures of a magainin peptide may include additional amino acids at the amino end or at the carboxyl end, or at both ends.

As representative examples of such magainin peptides, there may be mentioned peptides having the following primary sequences as given in the accompanying sequence listing as well as appropriate analogues and derivatives thereof:

(a) (SEQ ID NO:6) (OH) or (NH_2)
(Magainin I)

(b) (SEQ ID NO:7) (OH) or (NH_2)
(Magainin II)

(c) (SEQ ID NO:8) (OH) or (NH_2)
(Magainin III)

The following are examples of peptide derivatives or analogs of the basic structure:

(d) (SEQ ID NO:9) (OH) or (NH_2)

(e) (SEQ ID NO:10) (OH) or (NH_2)

(f) (SEQ ID NO:11) (OH) or (NH_2)

Magainin peptides are described in Proc. Natl. Acad Sci. Vol. 84 pp. 5449-53 (Aug. 87). The term "magainin peptides" as used herein refers to the basic magainin structure as well as derivatives and analogs thereof, including but not limited to the representative derivatives or analogs.

In accordance with a further embodiment, the peptide may be a PGLa peptide or an XPF peptide.

A PGLa peptide is either PGLa or an analogue or derivative thereof. The PGLa peptides preferably include the following basic peptide structure X_{14}:

$$- R_{11}-R_{17}-R_{12}-R_{11}-R_{14}-R_{14}-R_{11}-$$
$$R_{11}-R_{14}-R_{12}-R_{11}-R_{11}-R_{12}-R_{11}-$$
$$R_{11}-R_{11}-R_{12}-$$

where R_{11}, R_{12}, R_{14}, and R_{17} are as previously defined.

The PGLa peptides generally include at least seventeen amino acids and may include as many as forty amino acids. Accordingly, the hereinabove described basic peptide structure for a PGLa peptide may include additional amino acids at the amino end or at the carboxyl end or at both the amino and carboxyl end.

Thus, for example, a PGLa peptide may have the following structure:

$$-Y_{14}-X_{14}-$$

where X_{14} is as previously defined and

Y_{14} is

(i) R_{11};

(ii) R_{14}-R_{11}

where R_{11} and R_{14} are as previously defined.

For example, a PGLa peptide may also have the following structure:

-X_{14}-Z_{14}-

where X_{14} is as previously defined; and Z_{14} is:

(i) R_{11}; or

(ii) R_{11}-R_{11}

where R_{11} is as previously defined.

A PGLa peptide may also have the following structure:

$(Y_{14})_a$-X_{14}-$(Z_{14})_b$

where X_{14}; Y_{14} and Z_{14} are as previously defined, a is 0 or 1 and b is 0 or 1.

An XPF peptide is either XPF or an analogue or derivative thereof. The XPF peptides preferably include the following basic peptide structure X_{16}:

--R_{11}-R_{17}-R_{12}-R_{11}-R_{14}-R_{18}-R_{17}-

R_{11}-R_{14}-R_{12}-R_{11}-R_{11}-R_{12}-

R_{11}-R_{11}- R_{11}-R_{12}-$(R_{15})_n$-R_{11}--, wherein

R_{11}, R_{12}, R_{14}, R_{15} and R_{17} are as previously defined and R_{18} is glutamine or asparagine or a basic hydrophilic, or hydrophobic amino acid and, n is 0 or 1.

The XPF peptides generally include at least nineteen amino acids and may include up to forty amino acids. Accordingly, the hereinabove described basic peptide structure of XPF may include additional amino acids at the amino end, or at the carboxyl end or at both the amino and carboxyl ends.

Thus, for example, an XPF peptide may include the following structure:

-Y_{16}-X_{16}-

where X_{16} is as previously defined and Y_{16} is
(i) R_{11} or
(ii) R_{14}-R_{11}
where R_{11} and R_{14} are as previously defined.
An XPF peptide may include the following structure:
$-X_{16}-Z_{16}-$
where X_{16} is as previously defined and Z_{16} is
(i) R_{11}; or
(ii) R_{11}-R_{18}; or
(iii) R_{11}-R_{18}-Proline; or
(iv) R_{11}-R_{18}-Proline-R_{12}
An XPF peptide may also have the following structure:
$(Y_{16})_a$-X_{16}-$(Z_{16})_b$

where X_{16}, Y_{16} and Z_{16} are as previously defined: a is 0 or 1 and b is 0 or 1.

Preferred are XPF or PGLa peptides, which are characterized by the following primary amino acid sequences as given in the accompanying sequence listing:

PGLa : (SEQ ID NO:12) (NH_2)

XPF : (SEQ ID NO:13)

A review of XPF and PGLa can be found in Hoffman et al, EMBO J. 2:711-714, 1983; Andreu, et al, J. Biochem. 149:531-535, 1985; Gibson, et al J. Biol. Chem. 261:5341-5349, 1986; and Giovannini, et al, Biochem J. 243:113-120, 1987.

In accordance with yet another embodiment, the peptide may be a CPF peptide or appropriate analogue or derivative thereof.

CPF peptides as well as analogues and derivatives thereof are herein sometimes referred to collectively as CPF peptides.

The CPF peptide may be one which includes the following basic peptide structure X_{20};

$-R_{21}-R_{21}-R_{22}-R_{22}-R_{21}-R_{21}-R_{23}-R_{21}-$
$-R_{21}-R_{21}-R_{23}-R_{21}-R_{21}-R_{24}-R_{25}-R_{21}-$

wherein R_{21} is a hydrophobic amino acid;

R_{22} is a hydrophobic amino acid or a basic hydrophilic amino acid;

R_{23} is a basic hydrophilic amino acid;

R_{24} is a hydrophobic or neutral hydrophilic amino acid; and

R_{25} is a basic or neutral hydrophilic amino acid.

The hereinabove basic structure is hereinafter symbolically indicated as X_{20}.

The hydrophobic amino acids are Ala, Cys, Phe, Gly, Ile, Leu, Met, Val, Trp, Tyr, norleucine (Nle), norvaline (Nva), and cyclohexylalanine (Cha).

The neutral hydrophilic amino acids are Asn, Gln, Ser, Thr, and homoserine (Hse).

The basic hydrophilic amino acids are Lys, Arg, His, Orn, homoarginine (Har), 2,4-diaminobutyric acid (Dbu), and p-aminophenylalanine.

The CPF peptide may include only the hereinabove noted amino acids or may include additional amino acids at the amino and/or carboxyl end or both the amino and carboxyl end. In general, the peptide does not include more than 40 amino acids.

The CPF peptides including the above basic structure preferably have from 1 to 4 additional amino acids at the amino end.

Accordingly, such preferred peptides may be represented by the structural formula:

$$Y_{20} - X_{20} -$$

wherein X_{20} is the hereinabove described basic peptide structure and Y_{20} is

(i) $R_{25}-$, or

(ii) $R_{22}-R_{25}-$; or

(iii) R_{21}-R_{22}-R_{25}; or

(iv) R_{22}-R_{21}-R_{22}-R_{25}; preferably Glycine - R_{21}-R_{22}-R_{25}.

wherein R_{21}, R_{22} and R_{25} are as previously defined.

The carboxyl end of the basic peptide structure may also have additional amino acids which may range from 1 to 13 additional amino acids.

In a preferred embodiment, the basic structure may have from 1 to 7 additional amino acids at the carboxyl end, which may be represented as follows:

$-X_{20}$ - Z_{20} wherein

X is the hereinabove defined basic peptide structure and Z_{20} is

(i) R_{21}-, or

(ii) R_{21}-R_{21}-; or

(iii) R_{21}-R_{21}-R_{24}; or

(iv) R_{21}-R_{21}-R_{24}-R_{24}; or

(v) R_{21}-R_{21}-R_{24}-R_{24}-R_{26}; or

(vi) R_{21}-R_{21}-R_{24}-R_{24}-R_{26}-Gln; or

(vii) R_{21}-R_{21}-R_{24}-R_{24}-R_{26}-Gln-Gln, wherein R_{21} and R_{24} are as previously defined, and R_{26} is proline or a hydrophobic amino acid.

Preferred peptides may be represented by the following structural formula

$$(Y_{20})_a - X_{20} - (Z_{20})_b$$

wherein X_{20}, Y_{20} and Z_{20} are as previously defined and a is 0 or 1 and b is 0 or 1.

Representative examples of CPF peptides which may be employed, some of which have been described in the literature, include the following sequences as given in the accompanying sequence listing:

(SEQ ID NO:14)

(SEQ ID NO:15)

(SEQ ID NO:16)
(SEQ ID NO:17)
(SEQ ID NO:18)
(SEQ ID NO:19)
(SEQ ID NO:20)
(SEQ ID NO:21)
(SEQ ID NO:22)
(SEQ ID NO:23)
(SEQ ID NO:24)
(SEQ ID NO:25)
(SEQ ID NO:26)

A review of the CPF peptides can be found in Richter, K., Egger, R., and Kreil (1986) J. Biol. Chem 261, 3676-3680; Wakabayashi, T., Kato, H., and Tachibaba, S. (1985) Nucleic Acids Research 13, 1817-1828; Gibson, B.W., Poulter, L., Williams, D.H., and Maggio, J.E. (1986) J. Biol. Chem 261, 5341-5349.

In accordance with yet another embodiment, the peptide may include one of the following basic structures X_{31} through X_{37} wherein:

X_{31} is $-[R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}]-_n$;
X_{32} is $-[R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}]-_n$;
X_{33} is $-[R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}]-_n$;
X_{34} is $-[R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}]-_n$;
X_{35} is $-[R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}]-_n$;
X_{36} is $-[R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}]-_n$; and
X_{37} is $-[R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}]-_n$;

wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic, basic hydrophilic, or hydrophobic amino acid, and n is from 2 to 5.

The basic hydrophilic amino acids may be selected from the class consisting of Lys, Arg, His, Orn, homoarginine

(Har), 2,4-diaminobutyric acid (Dbu), and p-aminophenylalanine.

The hydrophobic amino acids may be selected from the class consisting of Ala, Cys, Phe, Gly, Ile, Leu, Met, Pro, Val, Trp and Tyr,norleucine (Nle), norvaline (Nva), and cyclohexylalanine (Cha).

The neutral hydrophilic amino acids may be selected from the class consisting of Asn, Gln, Ser, Thr, and homoserine (Hse).

In accordance with one embodiment, when the peptide includes the structure X_{31}, the peptide may include the following structure:

Y_{31}-X_{31}, wherein X_{31} is as hereinabove described, and Y_{31} is:

(i) R_{32};

(ii) R_{32}-R_{32};

(iii) R_{31}-R_{32}-R_{32};

(iv) R_{33}-R_{31}-R_{32}-R_{32};

(v) R_{32}-R_{33}-R_{31}-R_{32}-R_{32}; or

(vi) R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}, wherein R_{31}, R_{32}, and R_{33} are as hereinabove described

In accordance with another embodiment, when the peptide includes the structure X_{31}, the peptide may include the following structure:

X_{31}-Z_{31}, wherein X_{31} is as hereinabove described, and Z_{31} is:

(i) R_{31};

(ii) R_{31}-R_{32};

(iii) R_{31}-R_{32}-R_{32};

(iv) R_{31}-R_{32}-R_{32}-R_{33};

(v) R_{31}-R_{32}-R_{32}-R_{33}-R_{31}; or

(vi) R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}.

In accordance with yet another embodiment, the peptide may include the following structure:

$(Y_{31})_a$-X_{31}-$(Z_{31})_b$, wherein Y_{31} and Z_{31} are as previously defined, a is 0 or 1, and b is 0 or 1.

When the peptide includes the structure X_{32}, the peptide may include the following structure:

Y_{32} - X_{32}, wherein X_{32} is as hereinabove described, and Y_{32} is:

(i) R_{31};
(ii) R_{32}-R_{31};
(iii) R_{32}-R_{32}-R_{31};
(iv) R_{31}-R_{32}-R_{32}-R_{31};
(v) R_{33}-R_{31}-R_{32}-R_{32}-R_{31}; or
(vi) R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}.

In another embodiment, when the peptide includes the structure X_{32}, the peptide may include the following structure:

X_{32} - Z_{32}, wherein X_{32} is as hereinabove described, and Z_{32} is:

(i) R_{32};
(ii) R_{32}-R_{32};
(iii) R_{32}-R_{32}-R_{33};
(iv) R_{32}-R_{32}-R_{33}-R_{31};
(v) R_{32}-R_{32}-R_{33}-R_{31}-R_{32}; or
(vi) R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}.

In accordance with yet another embodiment, the peptide may include the following structure:

$(Y_{32})_a$ - X_{32} - $(Z_{32})_b$, wherein Y_{32} and Z_{32} are as previously defined, a is 0 or 1, and b is 0 or 1.

In accordance with another embodiment, when the peptide includes the structure X_{33}, the peptide may include the following structure:

Y_{33} - X_{33} wherein X_{33} is as hereinabove described, and Y_{33} is:

(i) R_{32};
(ii) R_{31}-R_{32};

(iii) R_{32}-R_{31}-R_{32};

(iv) R_{32}-R_{32}-R_{31}-R_{32};

(v) R_{31}-R_{32}-R_{32}-R_{31}-R_{32}; or

(vi) R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}, wherein R_{31}, R_{32}, and R_{33} are as hereinabove described.

In accordance with another embodiment, when the peptide includes the structure X_{33}, the peptide may include the following structure:

X_{33} - Z_{33} wherein X_{33} is as hereinabove described, and Z_{33} is:

(i) R_{32};

(ii) R_{32}-R_{33};

(iii) R_{32}-R_{33}-R_{31};

(iv) R_{32}-R_{33}-R_{31}-R_{32};

(v) R_{32}-R_{33}-R_{31}-R_{32}-R_{32}; or

(vi) R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}.

In accordance with yet another embodiment, the peptide may include the following structure:

$(Y_{33})_a$ - X_{33} - $(Z_{33})_b$, wherein Y_{33} and Z_{33} are as previously defined, a is 0 or 1, and b is 0 or 1.

In accordance with yet another embodiment, when the peptide includes the structure X_{34}, the peptide may include the following structure:

Y_{34} - X_{34}, wherein X_{34} is as hereinabove described, and Y_{34} is:

(i) R_{32};

(ii) R_{32}-R_{32};

(iii) R_{31}-R_{32}-R_{32};

(iv) R_{32}-R_{31}-R_{32}-R_{32};

(v) R_{32}-R_{32}-R_{31}-R_{32}-R_{32}; or

(vi) R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}, wherein R_{31}, R_{32} and R_{33} are as hereinabove described.

In accordance with another embodiment, when the peptide includes the structure X_{34}, the peptide may include the following structure:

X_{34}-Z_{34}, wherein X_{34} is as hereinabove described, and Z_{34} is:

(i) R_{33};

(ii) R_{33}-R_{31};

(iii) R_{33}-R_{31}-R_{32};

(iv) R_{33}-R_{31}-R_{32}-R_{32};

(v) R_{33}-R_{31}-R_{32}-R_{32}-R_{31}; or

(vi) R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}.

In accordance with yet another embodiment, the peptide may include the following structure:

$(Y_{34})_a$- X_{34}- $(Z_{34})_b$, wherein X_{34} and Z_{34} are as previously defined, a is 0 or 1, and b is 0 or 1.

In accordance with a further embodiment, when the peptide includes the structure X_{35}, the peptide may include the following structure:

Y_{35}-X_{35}, wherein X_{35} is as hereinabove described, and Y_{35} is:

(i) R_{33};

(ii) R_{32}-R_{33};

(iii) R_{32}-R_{32}-R_{33};

(iv) R_{31}-R_{32}-R_{32}-R_{33};

(v) R_{32}-R_{31}-R_{32}-R_{32}-R_{33}; or

(vi) R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}, wherein R_{31}, R_{32}, and R_{33} are as hereinabove described.

In accordance with another embodiment, when the peptide includes the structure X_{35}, the peptide may include the following structure:

X_{35} - Z_{35} wherein X_{35} is as hereinabove described, and Z_{35} is:

(i) R_{31};

(ii) R_{31}-R_{32};

(iii) R_{31}-R_{32}-R_{32};

(iv) R_{31}-R_{32}-R_{32}-R_{31};

(v) R_{31}-R_{32}-R_{32}-R_{31}-R_{32}; or

(vi) R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}.

In accordance with yet another embodiment, the peptide may include the following structure:

$(Y_{35})_a$- X_{35} $(Z_{35})_b$, wherein X_{35} and Z_{35} are as previously defined, a is 0 or 1, and b is 0 or 1.

In accordance with a further embodiment, when the peptide includes the structure X_{36}, the peptide may include the following structure:

Y_{36} - X_{36} wherein X_{36} is as hereinabove described, and Y_{36} is:

(i) R_{31};

(ii) R_{33}-R_{31};

(iii) R_{32}-R_{33}-R_{31};

(iv) R_{32}-R_{32}-R_{33}-R_{31};

(v) R_{31}-R_{32}-R_{32}-R_{33}-R_{31}; or

(vi) R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}, wherein R_{31}, R_{32}, and R_{33} are as hereinabove described.

In accordance with another embodiment, when the peptide includes the structure X_{36}, the peptide may include the following structure:

X_{36}-Z_{36}, wherein X_{36} is as hereinabove described, and Z_{36} is:

(i) R_{32};

(ii) R_{32}-R_{32};

(iii) R_{32}-R_{32}-R_{31};

(iv) R_{32}-R_{32}-R_{31}-R_{32};

(v) R_{32}-R_{32}-R_{31}-R_{32}-R_{32}; or

(vi) R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}.

In accordance with yet another embodiment, the peptide may include the following structure:

$(Y_{36})_a$- X_{36} $(Z_{36})_b$, wherein Y_{36} and Z_{36} are as previously defined, a is 0 or 1, and b is 0 or 1.

In accordance with one embodiment, when the peptide includes the structure X_{37}, the peptide may includes the structure Y_{37}-X_{37}, wherein X_{37} is as hereinabove described, and Y_{37} is:

(i) R_{32};

(ii) R_{31}-R_{32};

(iii) R_{33}-R_{31}-R_{32};

(iv) R_{32}-R_{33}-R_{31}-R_{32};

(v) R_{32}-R_{32}-R_{33}-R_{31}-R_{32}; or

(vi) R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}, wherein R_{31}, R_{32}, and R_{33} are as hereinabove described.

In accordance with a further embodiment, when the peptide includes the structure X_{37}, the peptide may include the following structure:

X_{37} - Z_{37} wherein X_{37} is as hereinabove described, and Z_{37} is:

(i) R_{32};

(ii) R_{32}-R_{31};

(iii) R_{32}-R_{31}-R_{32};

(iv) R_{32}-R_{31}-R_{32}-R_{32};

(v) R_{32}-R_{31}-R_{32}-R_{32}-R_{33}; or

(vi) R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}.

In accordance with yet another embodiment, the peptide may include the following structure:

$(Y_{37})_a$- X_{37} $(Z_{37})_b$, wherein Y_{37} and Z_{37} are as previously defined, a is 0 or 1, and b is 0 or 1.

In a preferred embodiment, n is 3, and most preferably the peptide is of one of the following structures as given in the accompanying sequence listing:

$(Lys\ Ile\ Ala\ Gly\ Lys\ Ile\ Ala)_3$ (SEQ ID NO:27).

$(Lys\ Ile\ Ala\ Lys\ Ile\ Ala\ Gly)_3$ (SEQ ID NO:28).

$(Lys\ Ile\ Ala\ Gly\ Lys\ Ile\ Gly)_3$ (SEQ ID NO:29).

(Lys Leu Ala Gly Lys Leu Ala)$_3$ (SEQ ID NO:30).
(Lys Phe Ala Gly Lys Phe Ala)$_3$ (SEQ ID NO:31).
(Lys Ala Leu Ser Lys Ala Leu)$_3$ (SEQ ID NO:32).
(Lys Leu Leu Lys Ala Leu Gly)$_3$ (SEQ ID NO:33).
(Lys Ala Ile Gly Lys Ala Ile)$_3$ (SEQ ID NO:34).
(Gly Ile Ala Lys Ile Ala Lys)$_3$ (SEQ ID NO:35).
(Lys Ile Ala Lys Ile Phe Gly)$_3$ (SEQ ID NO:36).
(Gly Ile Ala Arg Ile Ala Lys)$_3$ (SEQ ID NO:37).
(Lys Phe Ala Arg Ile Ala Gly)$_3$ (SEQ ID NO:38).
(Gly Phe Ala Lys Ile Ala Lys)$_3$ (SEQ ID NO:39).
(Lys Ile Ala Gly Orn Ile Ala)$_3$ (SEQ ID NO:40).
(Lys Ile Ala Arg Ile Ala Gly)$_3$ (SEQ ID NO:41).
(Orn Ile Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:42).
(Gly Ile Ala Arg Ile Phe Lys)$_3$ (SEQ ID NO:43).
(Lys Nle Ala Gly Lys Nle Ala)$_3$ (SEQ ID NO:44).
(Lys Nle Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:45).
(Lys Ile Ala Gly Lys Nle Ala)$_3$ (SEQ ID NO:46).
(Lys Nva Ala Gly Lys Nva Ala)$_3$ (SEQ ID NO:47).
(Lys Nva Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:48).
(Lys Leu Leu Ser Lys Leu Gly)$_3$ (SEQ ID NO:49).
(Lys Leu Leu Ser Lys Phe Gly)$_3$ (SEQ ID NO:50).
(Lys Ile Ala Gly Lys Nva Ala)$_3$ (SEQ ID NO:51).
(His Ile Ala Gly His Ile Ala)$_3$ (SEQ ID NO:52).
(Ala Gly Lys Ile Ala Lys Ile)$_3$ (SEQ ID NO:53).
(Ile Ala Lys Ile Ala Gly Lys)$_3$ (SEQ ID NO:54).
(Lys Ile Ala Gly Arg Ile Ala)$_3$ (SEQ ID NO:55).
(Arg Ile Ala Gly Arg Ile Ala)$_3$ (SEQ ID NO:56).
(Lys Val Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:57).
(Lys Ile Ala Gly Lys Val Ala)$_3$ (SEQ ID NO:58).
(Ala Lys Ile Ala Gly Lys Ile)$_3$ (SEQ ID NO:59).
(Orn Ile Ala Gly Orn Ile Ala)$_3$ (SEQ ID NO:60).
(Lys Phe Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:61).
(Lys Ile Ala Gly Lys Phe Ala)$_3$ (SEQ ID NO:62).
(Lys Cha Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:63).

(Lys Nle Ala Lys Ile Ala Gly)$_3$ (SEQ ID NO:64).

(Arg Ile Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:65).

(Har Ile Ala Gly Har Ile Ala)$_3$ (SEQ ID NO:66).

(Xaa Ile Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:67).

(Lys Ile Ala Gly Xaa Ile Ala)$_3$ (SEQ ID NO:68).

Lys Ile Ala (Lys Ile Ala Gly Lys Ile Ala)$_3$ (SEQ ID NO:69)

In (SEQ ID NO:67) and (SEQ ID NO:68), Xaa is p-aminophenylalanine.

In accordance with another embodiment, the amphiphilic peptide includes the following basic structure X_{40}:

R_{31}-R_{32}-R_{32}-R_{33}-R_{34}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{32}-R_{34}-R_{32}-R_{32},

wherein R_{31}, R_{32}, and R_{33} are as hereinabove described, and R_{34} is a basic hydrophilic or hydrophobic amino acid.

In accordance with one embodiment, the peptide may include the following structure:

Y_{40}-X_{40}, wherein X_{40} is as hereinabove described, and Y_{40} is:

(i) R_{32};

(ii) R_{32}-R_{32};

(iii) R_{34}-R_{32}-R_{32};

(iv) R_{33}-R_{34}-R_{32}-R_{32};

(v) R_{32}-R_{33}-R_{34}-R_{32}-R_{32};

(v) R_{32}-R_{32}-R_{33}-R_{34}-R_{32}-R_{32}, or

(vii) R_{31}-R_{32}-R_{32}-R_{33}-R_{34}-R_{32}-R_{32}, wherein R_{31}, R_{32}, R_{33} and R_{34} are as hereinabove described.

In accordance with another embodiment, the peptide may include the following structure:

X_{40}-Z_{40}, wherein X_{40} is as hereinabove described and Z_{40} is:

(i) R_{31};

(ii) R_{31}-R_{32};

(iii) R_{31}-R_{32}-R_{32};

(iv) R_{31}-R_{32}-R_{32}-R_{33};

(v) R_{31}-R_{32}-R_{32}-R_{33}-R_{34};

(vi) R_{31}-R_{32}-R_{32}-R_{33}-R_{34}-R_{32}; or

(vii) R_{31}-R_{32}-R_{32}-R_{33}-R_{34}-R_{32}-R_{32}, wherein R_{31}, R_{32}, R_{33}, and R_{34} are as hereinabove described.

In accordance with yet another embodiment the peptide may include the following structure:

$(Y_{40})_a$-X_{40}-$(Z_{40})_b$, wherein Y_{40} and Z_{40} are as previously defined, a is 0 or 1, and b is 0 or 1. In a preferred embodiment, the peptide has the following structural formula as given in the accompanying sequence listing:

(SEQ ID NO:70)

In another preferred embodiment, the peptide has the following structural formula as given in the accompanying sequence listing:

(SEQ ID NO:71)

In accordance with a further embodiment, the peptide has one of the one of the following structural formulae as given in the accompanying sequence listing:

(SEQ ID NO:72)

(SEQ ID NO:73)

(SEQ ID NO:74)

(SEQ ID NO:75)

(SEQ ID NO:76)

(SEQ ID NO:77)

(SEQ ID NO:78)

(SEQ ID NO:79)

(SEQ ID NO:80)

(SEQ ID NO:81)

(SEQ ID NO:82)

(SEQ ID NO:83)

(SEQ ID NO:84)

(SEQ ID NO:85)

(SEQ ID NO:86)

(SEQ ID NO:87)

In accordance with another embodiment, the peptide may include the following structural formula:

- (Lys Ile Ala Lys Lys Ile Ala)-$_n$, wherein n is from 2 to 5. Preferably, n is 3, and the peptide has the following structural formula:

(Lys Ile Ala Lys Lys Ile Ala)$_3$

(SEQ ID NO:88)

In accordance with another embodiment, the peptide may include the following structural formula:

-(Lys Phe Ala Lys Lys Phe Ala)-$_n$

wherein n is from 2 to 5.

Preferably, n is 3, and the peptide has the following structural formula:

(Lys Phe Ala Lys Lys Phe Ala)$_3$

(SEQ ID NO:89)

In accordance with another embodiment, the peptide may include the following structural formula:

-(Lys Phe Ala Lys Lys Ile Ala)-$_n$

wherein n is from 2 to 5. Preferably n is 3, and the peptide has the following structural formula:

(Lys Phe Ala Lys Lys Ile Ala)$_3$

(SEQ ID NO:90).

In accordance with another embodiment, the peptide may be selected from the group consisting of the following structural formulae as given in the accompanying sequence listing:

(SEQ ID NO:91)

(SEQ ID NO:92)

(SEQ ID NO:93)

(SEQ ID NO:94)

In accordance with yet another embodiment, the peptide may be a cecropin or sarcotoxin.

The term cecropins includes the basic structure as well as analogues and derivatives thereof. The cecropins and analogues and derivatives thereof are described in Ann. Rev. Microbiol. 1987, Vol. 41, pages 103-26, in particular page 108, and in Christensen, et al., PNAS Vol. 85, pgs. 5072-76, which are hereby incorporated by reference.

The term sarcotoxins includes the basic materials as well as analogues and derivatives thereof. The sarcotoxins and analogues and derivatives thereof are described in Molecular Entomology, pages 369-78, in particular page 375, Alan R. Liss, Inc. (1987), which is hereby incorporated by reference.

In another embodiment, the amphiphilic peptide includes the following basic structure X_{50}:

R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}.

R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

In one embodiment, the peptide includes the basic structure Y_{50}-X_{50} wherein X_{50} is as hereinabove described and Y_{50} is:

(i) R_{41};

(ii) R_{42}-R_{41}; or

(iii) R_{42}-R_{42}-R_{41}, wherein R_{41} and R_{42} are as hereinabove described.

In one embodiment, R_{41} is leucine. In another embodiment, R_{42} is lysine. Representative examples of such peptides include those having the following structures:

(SEQ ID NO: 95)

(SEQ ID NO: 96)

(SEQ ID NO: 97)

(SEQ ID NO: 98)

In accordance with another embodiment, the amphiphilic peptide includes the following basic structure X_{52}:

R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}, wherein R_{41} is a hydrophobic amino acid and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

In one embodiment R_{41} is leucine. In another embodiment, R_{42} is lysine.

In one embodiment, the peptide includes the basic structure Y_{52}-X_{52}, wherein X_{52} is as hereinabove described, and Y_{52} is:

(i) R_{42};
(ii) R_{41}-R_{42};
(iii) R_{41}-R_{41}-R_{42};
(iv) R_{42}-R_{41}-R_{41}-R_{42}; or
(v) R_{42}-R_{42}-R_{41}-R_{41}-R_{42}.

In one embodiment, the peptide may have the following structure:

Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu
5 10
Leu Lys Lys Leu Arg Arg
15
(SEQ ID NO:99)

In another embodiment, the peptide includes the basic structure X_{52} - Z_{52}, wherein X_{52} is as hereinabove described, and Z_{52} is:

(i) R_{41};
(ii) R_{41}-R_{41};
(iii) R_{41}-R_{41}-R_{42};
(iv) R_{41}-R_{41}-R_{42}-R_{42}; or
(v) R_{41}-R_{41}-R_{42}-R_{42}-R_{41};

In one embodiment, the peptide may have the following structure:

Lys Leu Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu Leu Lys Lys
Leu 5 10
15

(SEQ ID NO:100)

In another embodiment, the peptide may include the structure:

$(Y_{52})_a$ - X_{52} - $(Z_{52})_b$, wherein X_{52}, Y_{52} and Z_{52} are as hereinabove described, and a is 0 or 1, and b is 0 or 1.

In accordance with another embodiment, the peptide includes the following basic structure X_{54}:
$-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{43}-$,
wherein R_{41} and R_{42} are as hereinabove described, and R_{43} is a netural hydrophilic amino acid.

In one embodiment, the peptide may have the following structure:

(SEQ ID NO:101)

In another embodiment, the peptide may have the following structure:

(SEQ ID NO:102)

In accordance with yet another embodiment, the peptide includes the following basic structure X_{56}:
$R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{44}$, wherein R_{41} and R_{42} are as hereinabove described, and R_{44} is a neutral hydrophilic amino acid or proline.

In one embodiment, the peptide may include the following structure $Y_{56}-X_{56}$, wherein X_{56} is the basic peptide structure hereinabove described, and Y_{56} is:

(i) $-R_{41}$

(ii) $-R_{41}-R_{41}$;

(iii) $-R_{42}-R_{41}-R_{41}$;

(iv) $-R_{41}-R_{42}-R_{41}-R_{41}$;

(v) $-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}$;

(vi) $-R_{42}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}$; or

(vii) $-R_{42}-R_{42}-R_{41}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}$,

wherein R_{41} and R_{42} are as hereinabove described.

In one embodiment, the peptide may include the structure:

$X_{56}-Z_{56}$, wherein X_{56} is as hereinabove described, and Z_{56} is:

(i) $-R_{42}$;

(ii) $-R_{42}-R_{42}$;

(iii) $-R_{42}-R_{42}-R_{41}$;

(iv) $-R_{42}-R_{42}-R_{41}-R_{41}$;

(v) $-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}$;

(vi) $-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}$; or

(vii) $-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}$.

In a preferred embodiment, the peptide may have one of the following structures:

(SEQ ID NO:103); or

(SEQ ID NO:104).

In another embodiment, the peptide may have the structure $(Y_{56})_a$-X_{56}-$(Z_{56})_b$, wherein X_{56}, Y_{56}, and Z_{56} are as hereinabove described, a is 0 or 1, and b is 0 or 1.

In accordance with another embodiment, the peptide includes the following basic structure X_{58}:

R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{43},

wherein R_{41}, R_{42} and R_{43} are as hereinabove described.

In accordance with another embodiment, the peptide may include the structure Y_{58}-X_{58}, wherein X_{58} is as hereinabove described, and Y_{58} is:

(i) -R_{41};

(ii) -R_{42}-R_{41};

(iii) -R_{42}-R_{42}-R_{41};

(iv) -R_{41}-R_{42}-R_{42}-R_{41};

(v) -R_{41}-R_{41}-R_{42}-R_{42}-R_{41};

(vi) -R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}; or

(vii) -R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}, wherein R_{41} and R_{42} are as hereinabove described.

In another embodiment, the peptide includes the structure X_{58}-Z_{58}, wherein X_{58} is as hereinabove described, and Z_{58} is:

(i) -R_{41};

(ii) -R_{41}-R_{45};

(iii) -R_{41}-R_{45}-R_{45};

(iv) -R_{41}-R_{45}-R_{45}-R_{43};

(v) $-R_{41}-R_{45}-R_{45}-R_{43}-R_{41}$;

(vi) $-R_{41}-R_{45}-R_{45}-R_{43}-R_{41}-R_{43}$;

(vii) $-R_{41}-R_{45}-R_{45}-R_{43}-R_{41}-R_{43}-R_{43}$,

(viii) $-R_{41}-R_{45}-R_{45}-R_{43}-R_{41}-R_{43}-R_{43}-R_{45}$; or

(ix) $-R_{41}-R_{45}-R_{45}-R_{43}-R_{41}-R_{43}-R_{43}-R_{45}-R_{43}$,

wherein R_{41} and R_{43} are as hereinabove described, and R_{45} is proline.

In one embodiment, the peptide has the following structure:

(SEQ ID NO:105).

In one embodiment, the peptide may have the structure $(Y_{58})_a-X_{58}-(Z_{58})_b$, wherein X_{58}, Y_{58}, and Z_{58} are as hereinabove described, a is 0 or 1, and b is 0 or 1.

In accordance with another embodiment, the peptide includes the following basic structure X_{60}:

$R_{41}-R_{41}-R_{43}-R_{42}-R_{41}-R_{41}-R_{41}-R_{41}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-$

$R_{41}-R_{42}-R_{42}-R_{42}-R_{41}$, wherein R_{41}, R_{42}, and R_{43} are as hereinabove described. In one embodiment, the peptide may have the following structure:

(SEQ ID NO:106).

In another embodiment, the peptide may include the structure $X_{60}-Z_{60}$, wherein X_{60} is as hereinabove described, and Z_{60} is:

(i) $-R_{42}$;

(ii) $-R_{42}-R_{42}$;

(iii) $-R_{42}-R_{42}-R_{41}$;

(iv) $-R_{42}-R_{42}-R_{41}-R_{41}$;

(v) $-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}$;

(vi) $-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}$; or

(vii) $-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}$.

In accordance with yet another embodiment, the peptide has a structure selected from the group consisting of:

(a) $R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(b) $R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(c) $R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(d) $R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$; and

(e) $R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$,

wherein R_{41} and R_{42} are as hereinabove described.

In one embodiment, the peptide has the structure (a), and a representative example of such a structure is (SEQ ID NO:107), which is given in the accompanying sequence listing.

In another embodiment, the peptide has the structure (b), and a representative example of such a structure is (SEQ ID NO:108), which is given in the accompanying sequence listing.

In another embodiment, the peptide has the structure (c), and a representative example of such a structure is

(SEQ ID NO:109) as given the accompanying sequence listing.

In yet another embodiment, the peptide has the structure (d), and a representative example of such a structure is (SEQ ID NO:110) as given in the accompanying sequence listing.

In a further embodiment, the peptide has the structure (e), and representative examples of such a structure are (SEQ ID NO:111) and (SEQ ID NO:112) as given in the accompanying sequence listing.

In accordance with another embodiment, the peptide has the following structural formula:

(SEQ ID NO:113).

In accordance with another embodiment, the peptide is melittin.

Melittin is an amphipathic peptide consisting of 26 amino acid residues, and is isolated from honeybee (Apis mellifera) venom. The peptide is known to be cytolytic. See Habermann, et al., Hoppe-Seyler's Zeitschrift Physiol. Chem., Vol. 348, pgs. 37-50 (1987). Melittin has the following structural formula as represented by the three-letter amino acid code:

Gly Ile Gly Ala Val Leu Lys Val Leu

5

Thr Thr Gly Leu Pro Ala Leu Ile Ser

10 15

Trp Ile Lys Arg Lys Arg Gln Gln

20 25

(SEQ ID NO:114)

In another embodiment, the peptide purified in accordance with the present invention is an apidaecin. The term apidaecin as used herein includes the basic structure as well as analogues and derivaties thereof. Apidaecins are further described in European Patent Application No. 299,828.

In accordance with another embodiment, the peptide may be an amide - or carboxy-terminated peptide represented by the following structural formula, and the numbers below each amino acid residue refer to the position of the residue in the peptide:

Leu Lys Leu Leu Lys Lys Leu Leu Lys Lys Leu

1 2 3 4 5 6 7 8 9 10 11

Lys Lys Leu Leu Lys Lys Leu

12 13 14 15 16 17 18

(SEQ ID NO:115)

or the peptide may be an analogue of such peptide wherein at least one of amino acide residues 1 through 7, 9, 11, 12, 14, 16, or 18 is deleted from the peptide.

In one embodiment, at least one of amino acid residues 1, 3, 7, 9, 11, 12, 14, 16, or 18 is deleted from the peptide. In other embodiments, amino acid

residues 1 through 3, 1 through 4, 1 through 5, 1 through 6, and 1 through 7 are deleted from the peptide.

In preferred embodiments, amino acid residues 1 through 3 or 1 through 4 are deleted from the peptide, and such peptides have the following structural formulae:

(SEQ ID NO:116)

(SEQ ID NO:117)

In accordance with another embodiment, the peptide includes the following structural formula X_{62}:

R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-
R_{41}-R_{42}-R_{42},

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid. In one embodiment, R_{41} is leucine, and in another embodiment, R_{42} is lysine. In a preferred embodiment, the peptide has the following structure:

Leu Leu Lys Leu Leu Lys Lys Leu Leu Lys Lys Leu Lys Lys

5 10

(SEQ ID NO:118)

In accordance with another embodiment, the peptide includes the following structural formula X_{64}:

R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}
-R_{41}-R_{41},

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid. In one embodiment, R_{41} is leucine, and in another embodiment, R_{42} is lysine. In a preferred embodiment, the peptide has the following structural formula:

Lys Leu Leu Lys Lys Leu Lys Lys Leu Leu Lys Lys Leu Leu

5 10

(SEQ ID NO:119)

In another embodiment, the peptide includes the following structural formula X_{66}:

R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41},

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

In one embodiment, the peptide may include the following structure:

X_{66}-Z_{66}, wherein X_{66} is as hereinabove described and Z_{66} is:

(i) R_{42};

(ii) R_{42}-R_{41}; or

(iii) R_{42}-R_{41}-R_{41}.

In one embodiment, R_{41} is leucine, and in another embodiment, R_{42} is lysine. In a preferred embodiment, the peptide has the following structural formula:

Leu Leu Lys Lys Leu Lys Lys Leu Leu Lys Lys Leu Leu Lys

5 10

Leu Leu

15

(SEQ ID NO:120)

In yet another embodiment, the peptide may include the following structural formula X_{68}:

R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid. In one embodiment, R_{41} is leucine, and in another embodiment, R_{42} is lysine. In a preferred embodiment, the peptide has the following structural formula:

Lys Lys Leu Leu Lys Lys Leu Leu Lys Lys

5 10

Leu Leu Lys Lys Leu

15

(SEQ ID NO:121)

The peptide may also include acetyl or octanoyl groups at the N-terminal, such groups sometimes hereinafter being indicated as Ac- and Oct-, respectively.

In one embodiment, each amino acid residue of the peptide is a D-amino acid residue or a glycine residue. In another embodiment, each amino acid residue of the peptide is an L-amino acid residue or a glycine residue.

In yet another embodiment, the amino acid residues of the peptide which are not glycine residues may be a mixture of D-amino acid residues and L-amino acid residues.

The invention will now be described with respect to the following examples; however, the scope of the present invention is not intended to be limited thereby.

Example 1

A. Conjugation of peptides to dextran.

The following peptides:

(SEQ ID NO:89)-NH_2;

Ac-(SEQ ID NO:99)-NH_2;

Oct-(SEQ ID NO:111)-NH_2;

Ac-(SEQ ID NO:116)-NH_2;

Ac-(SEQ ID NO:117)-NH_2;

D-(SEQ ID NO:117)-NH_2, wherein each amino acid residue is a D-amino acid residue;

Ac-(SEQ ID NO:121)-NH_2;

(SEQ ID NO:123)-NH_2;

D-(SEQ ID NO:123)-NH_2, wherein each amino acid residue is a D-amino acid residue or a glycine residue; and

Ac-(SEQ ID NO:124)-NH_2

were conjugated to dextran. Such conjugation was carried out as follows:

1.0g of dextran (molecular weight 70,000-200,000) is dissolved in 50 ml of deionized water. 0.05 to 0.52g of sodium periodate is added. The reaction mixture is

stirred for 2 hours at room temperature, and then dialyzed over 4 liters of water for 4 hours using MWCO 1000. The oxidized dextran is mixed with 0.3g-1.0g of peptide which is dissolved in sodium bicarbonate buffer (pH 8.0-9.0), and left in a cold room for 6 to 8 hours. The mixture was then reduced with from 3 to 30ml of 6% sodium borohydride solution for 6 to 24 hours. The reaction is then acidified with acetic acid and dialyzed for 3 to 4 days over 10 liters using MWCO and lyophilized.

B. Conjugation of peptide to hetastarch.

Ac-(SEQ ID NO:117)-NH_2 was conjugated to hetastarch as follows:

15 ml of Hespan hetastarch (molecular weight 70,000) solution was cooled in an ice bath and 50 mg of 1-cyano-4-dimethylamino-pyridinium tetrafluoroborate was added, followed by 0.5ml of triethylamine solution. A mixture of ethanol/HCl (50m./0.5ml) was then added, and the precipitate was filtered and dissolved in 35 ml of saturated $NaHCO_3$ and water. The peptide was subsequently added as a powder to the reaction mixture and stirred at 4°C overnight. It was then dialyzed over 50,000 MWCO for 4 days over 10 liters of water and lyophilized.

C. Formation of a multiple antigenic peptide (MAP) conjugate.

Multiple antigenic peptides are peptides built onto a brached polylysine matrix. The polylysine matrix is comprised of 7 lysine residues built on a solid phase resin with a B-alanine spacer. Multiple antigenic peptides serve as a model for peptide-protein conjugates. The synthesis of the multiple antigenic peptide conjugate is carried out using solid phase methodology on an ABI-431 peptide synthesizer. (SEQ ID NO:122) is built on the matrix such that eight copies of (SEQ ID NO:122) are attached to the matrix. The cleavage and purification of the MAP peptides are carried out using standard methodology.

Example 2

Thirteen groups of CD-1 mice, with each group having 10 mice, were given actinomycin D in order to sensitize the mice to endotoxin. Each mouse ws injected with 20 micrograms of endotoxin. A control group of mice received an intraperitoneal challenge of from 0.1mg to 1.0mg of Endotoxin 0111:B4. The other groups of mice received an intraperitoneal challenge of from 0.1mg to 1.0mg of Endotoxin 0111:B4 and from 0.1mg to 7mg of one of the peptide conjugates described in Example 1. The conjugates had a peptide/polymer ratio of from 3% to 25% wt./wt. The conjugates were premixed with the endotoxin for 30 minutes prior to the intraperitoneal challenge. Survivors were assessed on a daily basis for 7 days. The

ratio of the number of survivors in each of the conjugate treatment groups at Day 2 and Day 7 to the number of survivors in the control groups is given in Table 1 below.

Table 1

Conjugate	Survivor Ratio Day 2	Day 7
(SEQ ID NO:89)-NH_2-dextran	3.3	9
Ac-(SEQ ID NO:99)-NH_2-dextran	3.3	8
Oct-(SEQ ID NO:111)-NH_2-dextran	10	10
Ac-(SEQ ID NO:116)-NH_2-dextran	4.5	4
Ac-(SEQ ID NO:117)-NH_2-dextran	5	8
D-(SEQ ID NO:117)-NH_2-dextran	9	8
Ac-(SEQ ID NO:117)-NH_2-hetastarch	2.5	1
Ac-(SEQ ID NO:121)-NH_2-dextran	3.3	9
(SEQ ID NO:122)-MAP	3.5	2
(SEQ ID NO:123)-NH_2-dextran	3.5	5
D-(SEQ ID NO:123)-NH_2-dextran	4	3
Oct-(SEQ ID NO:124)-NH_2-dextran	3.3	9

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Williams, Taffy J.
Hendi, Mukta
Rao, Meena

(ii) TITLE OF INVENTION: Treatment of Septic Shock with Conjugated Biologically Active Peptides

(iii) NUMBER OF SEQUENCES:

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Carella, Byrne, Bain, Gilfillan, Cecchi & Stewart
(B) STREET: 6 Becker Farm Road
(C) CITY: Roseland
(D) STATE: New Jersey
(E) COUNTRY: USA
(F) ZIP: 07068

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: 3.5 inch diskette
(B) COMPUTER: IBM PS/2
(C) OPERATING SYSTEM: PC-DOS
(D) SOFTWARE: DW4.V2

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: 07/987,443
(B) FILING DATE: 07-DEC-1992
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Olstein, Elliot M.
(B) REGISTRATION NUMBER: 24,025
(C) REFERENCE/DOCKET NUMBER: 421250-220

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 201-994-1700
(B) TELEFAX: 201-994-1744

(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO89/11290
(I) FILING DATE: 19-MAY-1989
(J) PUBLICATION DATE: 30-NOV-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
Ala Phe Ser Lys Ala Phe Ser Lys Ala Phe
                5                   10
Ser Lys Ala Phe Ser Lys Ala Phe Ser Lys
                15                  20
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO89/11290
(I) FILING DATE: 19-MAY-1989
(J) PUBLICATION DATE: 30-NOV-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Ala Phe Ser Lys Ala Phe Ser Lys Ala Phe
5 10
Ser Lys Ala Phe Ser Lys Ala Phe Ser Lys
15 20
Ala Phe Ser Lys

(2) INFORMATION FOR SEQ ID NO:3:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO89/11290
(I) FILING DATE: 19-MAY-1989
(J) PUBLICATION DATE: 30-NOV-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Phe Ser Lys Ala Phe Ser Lys Ala Phe Ser
5 10
Lys Ala Phe Ser Lys Ala
15

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 20 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: W089/11290

(I) FILING DATE: 19-MAY-1989

(J) PUBLICATION DATE: 30-NOV-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Ser Lys Ala Phe Ser Lys Ala Phe Ser Lys
5 10
Ala Phe Ser Lys Ala Phe Ser Lys Ala Phe
15 20

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO89/11290
(I) FILING DATE: 19-MAY-1989
(J) PUBLICATION DATE: 30-NOV-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Lys Ala Phe Ser Lys Ala Phe Ser Lys Ala
5 10
Phe Ser Lys Ala Phe Ser
15

(2) INFORMATION FOR SEQ ID NO:6:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Magainin I peptide.

(x) PUBLICATION INFORMATION:
(A) AUTHOR: Zasloff, Michael
(C) JOURNAL: Proc. Nat. Acad. Sci.
(D) VOLUME: 84
(F) PAGES: 5449-5453
(G) DATE: AUG - 1987
(H) DOCUMENT NUMBER: US 4810777
(I) FILING DATE: 04-MAR-1987
(J) PUBLICATION DATE: 07-MAR-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Gly Ile Gly Lys Phe Leu His Ser Ala Gly
5 10
Lys Phe Gly Lys Ala Phe Val Gly Glu Ile
15 20
Met Lys Ser

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 23 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Magainin II peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Zasloff, Michael

(C) JOURNAL: Proc. Nat. Acad. Sci.

(D) VOLUME: 84

(F) PAGES: 5449-5453

(G) DATE: AUG - 1987

(H) DOCUMENT NUMBER: US 4810777

(I) FILING DATE: 04-MAR-1987

(J) PUBLICATION DATE: 07-MAR-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Gly Ile Gly Lys Phe Leu His Ser Ala Lys
5 10

Lys Phe Gly Lys Ala Phe Val Gly Glu Ile
15 20

Met Asn Ser

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 22 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Magainin III peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Zasloff, Michael

(C) JOURNAL: Proc. Nat. Acad. Sci.

(D) VOLUME: 84

(F) PAGES: 5449-5453

(G) DATE: AUG - 1987

(H) DOCUMENT NUMBER: US 4810777

(I) FILING DATE: 04-MAR-1987

(J) PUBLICATION DATE: 07-MAR-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Gly Ile Gly Lys Phe Leu His Ser Ala Lys
5 10
Lys Phe Gly Lys Ala Phe Val Gly Glu Ile
15 20
Met Asn

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 22 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: magainin peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Zasloff, Michael

(C) JOURNAL: Proc. Nat. Acad. Sci.

(D) VOLUME: 84

(F) PAGES: 5449-5453

(G) DATE: AUG - 1987

(H) DOCUMENT NUMBER: US 4810777

(I) FILING DATE: 04-MAR-1987

(J) PUBLICATION DATE: 07-MAR-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Ile Gly Lys Phe Leu His Ser Ala Lys Lys
5 10
Phe Gly Lys Ala Phe Val Gly Glu Ile Met
15 20
Asn Ser

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: magainin peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Zasloff, Michael

(C) JOURNAL: Proc. Nat. Acad. Sci.

(D) VOLUME: 84

(F) PAGES: 5449-5453

(G) DATE: AUG - 1987

(H) DOCUMENT NUMBER: US 4810777

(I) FILING DATE: 04-MAR-1987

(J) PUBLICATION DATE: 07-MAR-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Gly Lys Phe Leu His Ser Ala Lys Lys Phe
5 10
Gly Lys Ala Phe Val Gly Glu Ile Met Asn
15 20
Ser

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 20 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: magainin peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Zasloff, Michael

(C) JOURNAL: Proc. Nat. Acad. Sci.

(D) VOLUME: 84

(F) PAGES: 5449-5453

(G) DATE: AUG - 1987

(H) DOCUMENT NUMBER: US 4810777

(I) FILING DATE: 04-MAR-1987

(J) PUBLICATION DATE: 07-MAR-1989

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Lys Phe Leu His Ser Ala Lys Lys Phe Gly
5 10
Lys Ala Phe Val Gly Glu Ile Met Asn Ser
15 20

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: PGLa peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Hoffman, et al.

(C) JOURNAL: EMBO J.

(D) VOLUME: 2

(F) PAGES: 711-714

(G) DATE: 1983

(A) AUTHOR: Andreu, et al.

(C) JOURNAL: Journal of Biochemistry

(D) VOLUME: 149

(F) PAGES: 531-535

(G) DATE: 1985

(A) AUTHOR: Gibson, et al.

(C) JOURNAL: J. Biol. Chem.

(D) VOLUME: 261

(F) PAGES: 5341-5349

(G) DATE: 1986

(A) AUTHOR: Giovannini, et al.

(C) JOURNAL: Biochem J.

(D) VOLUME: 243

(F) PAGES: 113-120

(G) DATE: 1987

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Gly Met Ala Ser Lys Ala Gly Ala Ile Ala
5 10
Gly Lys Ile Ala Lys Val Ala Leu Lys Ala
15 20
Leu

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 25 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: XPF peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Hoffman, et al.l

(C) JOURNAL: EMBO J.

(D) VOLUME: 2

(F) PAGES: 711-714

(G) DATE: 1983

(A) AUTHOR: Andreu, et al.

(C) JOURNAL: Journal of Biochemistry

(D) VOLUME: 149

(F) PAGES: 531-535

(G) DATE: 1985

(A) AUTHOR: Gibson, et al.

(C) JOURNAL: J. Biol. Chem.

(D) VOLUME: 261

(F) PAGES: 5341-5349

(G) DATE: 1986
(A) AUTHOR: Giovannini, et al.
(C) JOURNAL: Biochem J.
(D) VOLUME: 243
(F) PAGES: 113-120
(G) DATE: 1987

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Gly Trp Ala Ser Lys Ile Gly Gln Thr Leu
5 10
Gly Lys Ile Ala Lys Val Gly Leu Lys Glu
15 20
Leu Ile Gln Pro Lys
25

(2) INFORMATION FOR SEQ ID NO:14:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:
(A) AUTHOR: Richter, K.
Egger, R.
Kreil
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 3676-3680

(G) DATE: 1986
(A) AUTHOR: Wakabayashi, T.
Kato, H.
Tachibaba, S.
(C) JOURNAL: Nucleic Acids Research
(D) VOLUME: 13
(F) PAGES: 1817-1828
(G) DATE: 1985
(A) AUTHOR: Gibson, B.W.
Poulter, L.
Williams, D.H.
Maggio, J.E.
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986
(H) DOCUMENT NUMBER: WO90/04407
(I) FILING DATE: 16-OCT-1989
(J) PUBLICATION DATE: 03-MAY-1990

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Gly Phe Gly Ser Phe Leu Gly Leu Ala Leu
5 10
Lys Ala Ala Leu Lys Ile Gly Ala Asn Ala
15 20
Leu Gly Gly Ala Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:15:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:
(A) AUTHOR: Richter, K
Egger, R.
Kreil
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 3676-3680
(G) DATE: 1986
(A) AUTHOR: Wakabayashi, T.
Kato, H.
Tachibaba, S.
(C) JOURNAL: Nucleic Acids Research
(D) VOLUME: 13
(F) PAGES: 1817-1828
(G) DATE: 1985
(A) AUTHOR: Gibson, B.W.
Poulter, L.
Williams, D.H.
Maggio, J.E.
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986
(H) DOCUMENT NUMBER: WO90/04407
(I) FILING DATE: 16-OCT-1989
(J) PUBLICATION DATE: 03-MAY-1990

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Gly Leu Ala Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Gly Leu Lys Ile Gly Ala His Leu
15 20
Leu Gly Gly Ala Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 27 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Richter, K.
Egger, R.
Kreil

(C) JOURNAL: J. Biol. Chem.

(D) VOLUME: 261

(F) PAGES: 3676-3680

(G) DATE: 1986

(A) AUTHOR: Wakabayashi, T.
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(C) JOURNAL: Nucleic Acids Research

(D) VOLUME: 13

(F) PAGES: 1817-1828

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(A) AUTHOR: Gibson, B.W.
Poulter, L.
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Maggio, J.E.
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(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986
(H) DOCUMENT NUMBER: WO90/04407
(I) FILING DATE: 16-OCT-1989
(J) PUBLICATION DATE: 03-MAY-1990

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Gly Leu Ala Ser Leu Leu Gly Lys Ala Leu
5 10
Lys Ala Gly Leu Lys Ile Gly Thr His Phe
15 20
Leu Gly Gly Ala Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Richter, K.
Egger, R.
Kreil
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 3676-3680
(G) DATE: 1986
(A) AUTHOR: Wakabayashi, T.
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(C) JOURNAL: Nucleic Acids Research
(D) VOLUME: 13
(F) PAGES: 1817-1828
(G) DATE: 1985
(A) AUTHOR: Gibson, B.W.
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Maggio, J.E.
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(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986
(H) DOCUMENT NUMBER: W090/04407
(I) FILING DATE: 16-OCT-1989
(J) PUBLICATION DATE: 03-MAY-1990

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Gly Leu Ala Ser Leu Leu Gly Lys Ala Leu
5 10
Lys Ala Thr Leu Lys Ile Gly Thr His Phe
15 20
Leu Gly Gly Ala Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 27 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Richter, K.
Egger, R.
Kreil

(C) JOURNAL: J. Biol. Chem.

(D) VOLUME: 261

(F) PAGES: 3676-3680

(G) DATE: 1986

(A) AUTHOR: Wakabayashi, T.
Kato, H.
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(C) JOURNAL: Nucleic Acids Research

(D) VOLUME: 13

(F) PAGES: 1817-1828

(G) DATE: 1985

(A) AUTHOR: Gibson, B.W.
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(C) JOURNAL: J. Biol. Chem.

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(G) DATE: 1986
(H) DOCUMENT NUMBER: W090/04407
(I) FILING DATE: 16-OCT-1989
(J) PUBLICATION DATE: 03-MAY-1990

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Gly Phe Ala Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Ala Leu Lys Ile Gly Ala Asn Met
15 20
Leu Gly Gly Thr Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:19:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:
(A) AUTHOR: Richter, K.
Egger, R.
Kreil
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 3676-3680
(G) DATE: 1986
(A) AUTHOR: Wakabayashi, T.

Kato, H.
Tachibaba, S.
(C) JOURNAL: Nucleic Acids Research
(D) VOLUME: 13
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(G) DATE: 1985
(A) AUTHOR: Gibson, B.W.
Poulter, L.
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(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986
(H) DOCUMENT NUMBER: W090/04407
(I) FILING DATE: 16-OCT-1989
(J) PUBLICATION DATE: 03-MAY-1990

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Gly Phe Gly Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Ala Leu Lys Ile Gly Ala Asn Ala
15 20
Leu Gly Gly Ala Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:
(A) AUTHOR: Richter, K.
Egger, R.
Kreil
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 3676-3680
(G) DATE: 1986
(A) AUTHOR: Wakabayashi, T.
Kato, H.
Tachibaba, S.
(C) JOURNAL: Nucleic Acids Research
(D) VOLUME: 13
(F) PAGES: 1817-1828
(G) DATE: 1985
(A) AUTHOR: Gibson, B.W.
Poulter, L.
Williams, D.H.
Maggio, J.E.
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
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(G) DATE: 1986
(H) DOCUMENT NUMBER: WO90/04407
(I) FILING DATE: 16-OCT-1989
(J) PUBLICATION DATE: 03-MAY-1990

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Gly Phe Gly Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Ala Leu Lys Ile Gly Ala Asn Ala
15 20
Leu Gly Gly Ser Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 27 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Richter, K.
Egger, R.
Kreil

(C) JOURNAL: J. Biol. Chem.

(D) VOLUME: 261

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(G) DATE: 1986

(A) AUTHOR: Wakabayashi, T.
Kato, H.
Tachibaba, S.

(C) JOURNAL: Nucleic Acids Research

(D) VOLUME: 13

(F) PAGES: 1817-1828

(G) DATE: 1985
(A) AUTHOR: Gibson, B.W.
Poulter, L.
Williams, D.H.
Maggio, J.E.
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
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(G) DATE: 1986
(H) DOCUMENT NUMBER: W090/04407
(I) FILING DATE: 16-OCT-1989
(J) PUBLICATION DATE: 03-MAY-1990

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Gly Phe Ala Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Ala Leu Lys Ile Gly Ala Asn Leu
15 20
Leu Gly Gly Thr Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:22:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Richter, K.
Egger, R.
Kreil
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 3676-3680
(G) DATE: 1986
(A) AUTHOR: Wakabayashi, T.
Kato, H.
Tachibaba, S.
(C) JOURNAL: Nucleic Acids Research
(D) VOLUME: 13
(F) PAGES: 1817-1828
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(A) AUTHOR: Gibson, B.W.
Poulter, L.
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Maggio, J.E.
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Gly Phe Ala Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Ala Leu Lys Ile Gly Ala Asn Ala
15 20
Leu Gly Gly Ala Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:23:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:
(A) AUTHOR: Richter, K.
Egger, R.
Kreil
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 3676-3680
(G) DATE: 1986
(A) AUTHOR: Wakabayashi, T.
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(C) JOURNAL: Nucleic Acids Research
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(F) PAGES: 1817-1828
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(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Gly Phe Ala Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Ala Leu Lys Ile Gly Ala Asn Met
15 20
Leu Gly Gly Ala Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 27 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:

(A) AUTHOR: Richter, K.
Egger, R.
Kreil

(C) JOURNAL: J. Biol. Chem.

(D) VOLUME: 261

(F) PAGES: 3676-3680

(G) DATE: 1986

(A) AUTHOR: Wakabayashi, T.
Kato, H.
Tachibaba, S.

(C) JOURNAL: Nucleic Acids Research

(D) VOLUME: 13

(F) PAGES: 1817-1828

(G) DATE: 1985
(A) AUTHOR: Gibson, B.W.
Poulter, L.
Williams, D.H.
Maggio, J.E.
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Gly Phe Gly Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Ala Leu Lys Ile Gly Ala Asn Ala
15 20
Leu Gly Gly Ser Leu Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:25:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:
(A) AUTHOR: Richter, K.
Egger, R.
Kreil

(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 3676-3680
(G) DATE: 1986
(A) AUTHOR: Wakabayashi, T.
Kato, H.
Tachibaba, S.
(C) JOURNAL: Nucleic Acids Research
(D) VOLUME: 13
(F) PAGES: 1817-1828
(G) DATE: 1985
(A) AUTHOR: Gibson, B.W.
Poulter, L.
Williams, D.H.
Maggio, J.E.
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Gly Phe Gly Ser Phe Leu Gly Lys Ala Leu
5 10
Lys Ala Gly Leu Lys Ile Gly Thr Asn Phe
15 20
Leu Gly Gly Ala Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:26:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: CPF peptide.

(x) PUBLICATION INFORMATION:
(A) AUTHOR: Richter, K
Egger, R.
Kreil
(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
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(C) JOURNAL: J. Biol. Chem.
(D) VOLUME: 261
(F) PAGES: 5341-5349
(G) DATE: 1986

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Gly Leu Ala Ser Leu Leu Gly Lys Ala Leu
5 10

Lys Ala Ala Leu Lys Ile Gly Ala Asn Ala
15 20
Leu Gly Gly Ser Pro Gln Gln
25

(2) INFORMATION FOR SEQ ID NO:27:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:
Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Lys Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:28:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:
Lys Ile Ala Lys Ile Ala Gly Lys Ile Ala
5 10

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
15 20
Gly

(2) INFORMATION FOR SEQ ID NO:29:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:
Lys Ile Ala Gly Lys Ile Gly Lys Ile Ala
5 10
Gly Lys Ile Gly Lys Ile Ala Gly Lys Ile
15 20
Gly

(2) INFORMATION FOR SEQ ID NO:30:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:
Lys Leu Ala Gly Lys Leu Ala Lys Leu Ala
5 10

Gly Lys Leu Ala Lys Leu Ala Gly Lys Leu
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:31:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:
Lys Phe Ala Gly Lys Phe Ala Lys Phe Ala
5 10
Gly Lys Phe Ala Lys Phe Ala Gly Lys Phe
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
Lys Ala Leu Ser Lys Ala Leu Lys Ala Leu
5 10

Ser Lys Ala Leu Lys Ala Leu Ser Lys Ala
15 20
Leu

(2) INFORMATION FOR SEQ ID NO:33:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:
Lys Leu Leu Lys Ala Leu Gly Lys Leu Leu
5 10
Lys Ala Leu Gly Lys Leu Leu Lys Ala Leu
15 20
Gly

(2) INFORMATION FOR SEQ ID NO:34:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:
Lys Ala Ile Gly Lys Ala Ile Lys Ala Ile
5 10

Gly Lys Ala Ile Lys Ala Ile Gly Lys Ala
15 20
Ile

(2) INFORMATION FOR SEQ ID NO:35:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:
Gly Ile Ala Lys Ile Ala Lys Gly Ile Ala
5 10
Lys Ile Ala Lys Gly Ile Ala Lys Ile Ala
15 20
Lys

(2) INFORMATION FOR SEQ ID NO:36:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:
Lys Ile Ala Lys Ile Phe Gly Lys Ile Ala
5 10

Lys Ile Phe Gly Lys Ile Ala Lys Ile Phe
15 20
Gly

(2) INFORMATION FOR SEQ ID NO:37:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:
Gly Ile Ala Arg Ile Ala Lys Gly Ile Ala
5 10
Arg Ile Ala Lys Gly Ile Ala Arg Ile Ala
15 20
Lys

(2) INFORMATION FOR SEQ ID NO:38:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:
Lys Phe Ala Arg Ile Ala Gly Lys Phe Ala
5 10

Arg Ile Ala Gly Lys Phe Ala Arg Ile Ala
15 20
Gly

(2) INFORMATION FOR SEQ ID NO:39:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:
Gly Phe Ala Lys Ile Ala Lys Gly Phe Ala
5 10
Lys Ile Ala Lys Gly Phe Ala Lys Ile Ala
15 20
Lys

(2) INFORMATION FOR SEQ ID NO:40:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is ornithine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:
Lys Ile Ala Gly Xaa Ile Ala Lys Ile Ala
5 10

Gly Xaa Ile Ala Lys Ile Ala Gly Xaa Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:41:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:
Lys Ile Ala Arg Ile Ala Gly Lys Ile Ala
5 10
Arg Ile Ala Gly Lys Ile Ala Arg Ile Ala
15 20
Gly

(2) INFORMATION FOR SEQ ID NO:42:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is ornithine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Xaa Ile Ala Gly Lys Ile Ala Xaa Ile Ala
5 10
Gly Lys Ile Ala Xaa Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Gly Ile Ala Arg Ile Phe Lys Gly Ile Ala
5 10
Arg Ile Phe Lys Gly Ile Ala Arg Ile Phe
15 20
Lys

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa is norleucine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Lys Xaa Ala Gly Lys Xaa Ala Lys Xaa Ala
5 10
Gly Lys Xaa Ala Lys Xaa Ala Gly Lys Xaa
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa is norleucine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Lys Xaa Ala Gly Lys Ile Ala Lys Xaa Ala
5 10
Gly Lys Ile Ala Lys Xaa Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norleucine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Lys Ile Ala Gly Lys Xaa Ala Lys Ile Ala
5 10
Gly Lys Xaa Ala Lys Ile Ala Gly Lys Xaa
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:47:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norvaline.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Lys Xaa Ala Gly Lys Xaa Ala Lys Xaa Ala
5 10
Gly Lys Xaa Ala Lys Xaa Ala Gly Lys Xaa
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:48:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norvaline.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```
Lys Xaa Ala Gly Lys Ile Ala Lys Xaa Ala
                5                  10
Gly Lys Ile Ala Lys Xaa Ala Gly Lys Xaa
                15                 20
Ala
```

(2) INFORMATION FOR SEQ ID NO:49:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
Lys Leu Leu Ser Lys Leu Gly Lys Leu Leu
                5                  10
Ser Lys Leu Gly Lys Leu Leu Ser Lys Leu
                15                 20
Gly
```

(2) INFORMATION FOR SEQ ID NO:50:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

```
Lys Leu Leu Ser Lys Phe Gly Lys Leu Leu
                5                   10
Ser Lys Phe Gly Lys Leu Leu Ser Lys Phe
                15                  20
Gly
```

(2) INFORMATION FOR SEQ ID NO:51:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norvaline.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```
Lys Ile Ala Gly Lys Xaa Ala Lys Ile Ala
                5                   10
Gly Lys Xaa Ala Lys Ile Ala Gly Lys Xaa
                15                  20
Ala
```

(2) INFORMATION FOR SEQ ID NO:52:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```
His Ile Ala Gly His Ile Ala His Ile Ala
                5                  10
Gly His Ile Ala His Ile Ala Gly His Ile
                15                 20
Ala
```

(2) INFORMATION FOR SEQ ID NO:53:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```
Ala Gly Lys Ile Ala Lys Ile Ala Gly Lys
               5                  10
Ile Ala Lys Ile Ala Gly Lys Ile Ala Lys
               15                 20
Ile
```

(2) INFORMATION FOR SEQ ID NO:54:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Ile Ala Lys Ile Ala Gly Lys Ile Ala Lys
5 10
Ile Ala Gly Lys Ile Ala Lys Ile Ala Gly
15 20
Lys

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Lys Ile Ala Gly Arg Ile Ala Lys Ile Ala
5 10
Gly Arg Ile Ala Lys Ile Ala Gly Arg Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Arg Ile Ala Gly Arg Ile Ala Arg Ile Ala
5 10
Gly Arg Ile Ala Arg Ile Ala Gly Arg Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Lys Val Ala Gly Lys Ile Ala Lys Val Ala
5 10
Gly Lys Ile Ala Lys Val Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Lys Ile Ala Gly Lys Val Ala Lys Ile Ala
5 10
Gly Lys Val Ala Lys Ile Ala Gly Lys Val
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Ala Lys Ile Ala Gly Lys Ile Ala Lys Ile
5 10
Ala Gly Lys Ile Ala Lys Ile Ala Gly Lys
15 20
Ile

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa is ornithine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Xaa Ile Ala Gly Xaa Ile Ala Xaa Ile Ala
5 10
Gly Xaa Ile Ala Xaa Ile Ala Gly Xaa Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Lys Phe Ala Gly Lys Ile Ala Lys Phe Ala
5 10
Gly Lys Ile Ala Lys Phe Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Lys Ile Ala Gly Lys Phe Ala Lys Ile Ala
5 10
Gly Lys Phe Ala Lys Ile Ala Gly Lys Phe
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa is cyclohexylalanine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Lys Xaa Ala Gly Lys Ile Ala Lys Xaa Ala
5 10
Gly Lys Ile Ala Lys Xaa Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norleucine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

```
Lys Xaa Ala Lys Ile Ala Gly Lys Xaa Ala
                5                   10
Lys Ile Ala Gly Lys Xaa Ala Lys Ile Ala
                15                  20
Gly
```

(2) INFORMATION FOR SEQ ID NO:65:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 AMINO ACIDS
(B) TYPE: amino acids
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

```
Arg Ile Ala Gly Lys Ile Ala Arg Ile Ala
                5                   10
Gly Lys Ile Ala Arg Ile Ala Gly Lys Ile
                15                  20
Ala
```

(2) INFORMATION FOR SEQ ID NO:66:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is homoarginine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Xaa Ile Ala Gly Xaa Ile Ala Xaa Ile Ala
5 10
Gly Xaa Ile Ala Xaa Ile Ala Gly Xaa Ile
15 20
Ala

(2)INFORMATION FOR SEQ ID NO:67:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE: Xaa is p-aminophenylalanine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Xaa Ile Ala Gly Lys Ile Ala Xaa Ile Ala
5 10
Gly Lys Ile Ala Xaa Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:68:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE: Xaa is p-aminophenylalanine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Lys Ile Ala Gly Xaa Ile Ala Lys Ile Ala
5 10
Gly Xaa Ile Ala Lys Ile Ala Gly Xaa Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Lys Ile Ala Lys Ile Ala Gly Lys Ile Ala
5 10
Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
15 20
Gly Lys Ile Ala

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Lys Leu Ala Ser Lys Ala Gly Lys Ile Ala Gly
5 10
Lys Ile Ala Lys Val Ala Leu Lys Ala Leu
15 20

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa is ornithine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala Gly
5 10
Xaa Ile Ala Lys Ile Ala Gly Lys Ile Ala
15 20

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Arg Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa is norleucine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Xaa Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norvaline.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Xaa Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:75:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is ornithine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Lys Phe Ala Gly Lys Phe Ala Lys Phe Ala Gly
5 10
Xaa Phe Ala Lys Phe Ala Gly Lys Phe Ala
15 20

(2) INFORMATION FOR SEQ ID NO:76:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is ornithine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
Lys Ile Ala Gly Lys Phe Ala Lys Ile Ala
                5                   10
Gly Xaa Phe Ala Lys Ile Ala Gly Lys Phe
                15                  20
Ala
```

(2) INFORMATION FOR SEQ ID NO:77:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa at residues 6, 13, and 20 is norleucine; Xaa at residue 12 is ornithine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```
Lys Ile Ala Gly Lys Xaa Ala Lys Ile Ala
                5                   10
Gly Xaa Xaa Ala Lys Ile Ala Gly Lys Xaa
                15                  20
Ala
```

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Lys Met Ala Ser Lys Ala Gly Lys Ile Ala
5 10
Gly Lys Ile Ala Lys Val Ala Leu Lys Ala
15 20
Leu

(2) INFORMATION FOR SEQ ID NO:79:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79

Lys Ile Ala Ser Lys Ala Gly Lys Ile Ala
5 10
Gly Lys Ile Ala Lys Val Ala Leu Lys Ala Leu
15 20

(2) INFORMATION FOR SEQ ID NO:80:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norleucine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
Lys Ile Ala Ser Lys Ala Gly Lys Xaa Ala
                5                   10
Gly Lys Ile Ala Lys Val Ala Leu Lys Ala Leu
                15                  20
```

(2) INFORMATION FOR SEQ ID NO:81:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norleucine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
Lys Leu Ala Ser Lys Ala Gly Lys Xaa Ala
                5                   10
Gly Lys Ile Ala Lys Val Ala Leu Lys Ala
                15                  20
Leu
```

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is norleucine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
Lys Xaa Ala Ser Lys Ala Gly Lys Xaa Ala
                5                   10
Gly Lys Ile Ala Lys Val Ala Leu Lys Ala Leu
                15                  20
```

(2) INFORMATION FOR SEQ ID NO:83:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: Xaa is p-aminophenylalanine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Xaa Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Lys Ile Ala Gly Ala Ile Ala Lys Ile Ala
5 10
Gly Lys Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Ala Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Lys Ile Ala Lys Ile Ala Gly Ala Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Lys Leu Ala Ser Lys Ala Ala Lys Ile Ala

5 10
Ala Lys Ile Ala Lys Val Ala Leu Lys Ala
10 20
Leu

(2) INFORMATION FOR SEQ ID NO:88:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:
Lys Ile Ala Lys Lys Ile Ala Lys Ile Ala
5 10
Lys Lys Ile Ala Lys Ile Ala Lys Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:89:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:
Lys Phe Ala Lys Lys Phe Ala Lys Phe Ala
5 10
Lys Lys Phe Ala Lys Phe Ala Lys Lys Phe

15 20

Ala

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Lys Phe Ala Lys Lys Ile Ala Lys Phe Ala
5 10
Lys Lys Ile Ala Lys Phe Ala Lys Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Ala Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Lys Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Lys Ile Ala Gly Lys Ile Ala Ala Ile Ala
5 10
Gly Lys Ile Ala Lys Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Lys Ile Ala Gly Lys Ile Ala Lys Ile Ala
5 10
Gly Lys Ile Ala Ala Ile Ala Gly Lys Ile
15 20
Ala

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 21 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Gly Met Ala Ser Lys Ala Gly Lys Ile Ala
5 10
Gly Lys Ile Ala Lys Val Ala Leu Lys Ala
15 20
Leu

(2) INFORMATION FOR SEQ ID NO:95:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:95:

Leu Lys Lys Leu Lys Lys Leu Leu Lys Leu
5 10
Leu

(2) INFORMATION FOR SEQ ID NO:96:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:96:

Leu Leu Lys Lys Leu Lys Lys Leu Leu Lys
5 10
Leu Leu

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:97:

Lys Leu Leu Lys Lys Leu Lys Lys Leu Leu
5 10
Lys Leu Leu

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:98:

Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu
5 10
Leu Lys Leu Leu

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu Leu Lys Lys Leu Arg Arg
5 10 15

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:100:

Lys Leu Lys Lys Leu Leu Lys Lys Leu Lys
5 10
Lys Leu Leu Lys Leu Leu
15

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 15 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

Leu Lys Lys Leu Leu Lys Lys Leu Lys Lys
5 10
Leu Leu Lys Lys Asn
15

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 15 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa is homoserine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Leu Lys Lys Leu Leu Lys Lys Leu Lys Lys
5 10
Leu Leu Lys Lys Xaa
15

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

Leu Lys Leu Leu Lys Lys Leu Leu Lys Lys
5 10

Asn Lys Lys Leu Leu Lys Lys Leu
15

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 18 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Leu Lys Leu Leu Lys Lys Leu Leu Lys Lys
5 10

Pro Lys Lys Leu Leu Lys Lys Leu
15

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 22 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

Leu Leu Lys Lys Leu Lys Lys Leu Leu Lys
5 10
Lys Leu Gln Gly Pro Pro Gln Gly Gln Ser
15 20
Pro Gln

(2) INFORMATION FOR SEQ ID NO:106:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:
Leu Ala Ser Lys Ala Gly Ala Ile Ala Gly
5 10
Lys Ile Ala Lys Lys Leu Leu Lys Lys Leu
15 20

(2) INFORMATION FOR SEQ ID NO:107:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:
Leu Lys Lys Leu Lys Lys Leu
5

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 8 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

Leu Leu Lys Lys Leu Lys Lys Leu
5

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Lys Leu Leu Lys Lys Leu Lys Lys Leu
5

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu
5 10

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 11 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Leu Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu
5 10

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 11 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

Ala Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu
5 10

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 14 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

Leu Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu
5 10
Leu Lys Arg

(2) INFORMATION FOR SEQ ID NO:114:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(vi) ORIGINAL SOURCE
(A) ORGANISM: Apis mellifera

(vii) FEATURE

(A) NAME/KEY: melittin peptide

(x) PUBLICATION INFORMATION:
(A) AUTHORS: Habermann, E.
Jentsch, J.
(B) TITLE: Sequenzanalyse des Melittins aus den tryptischen and peptischen Spaltstucken
(C) JOURNAL: Hoppe-Seyler's Zeitschrift Physiol. Chem.

(D) VOLUME: 348
(F) PAGES: 37-50
(G) DATE: 1987

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Gly Ile Gly Ala Val Leu Lys Val Leu
5
Thr Thr Gly Leu Pro Ala Leu Ile Ser Trp
10 15
Ile Lys Arg Lys Arg Gln Gln
20 25

(2) INFORMATION FOR SEQ ID NO:115:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Leu Lys Leu Leu Lys Lys Leu Leu Lys Lys
5 10
Leu Lys Lys Leu Leu Lys Lys Leu
15

(2) INFORMATION FOR SEQ ID NO:116:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: C-terminal amide, may be acetylated at N-terminus.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

Leu Lys Lys Leu Leu Lys Lys Leu Lys Lys
5 10
Leu Leu Lys Lys Leu
15

(2) INFORMATION FOR SEQ ID NO:117:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(D) OTHER INFORMATION: C-terminal amide, may be acetylated at N-terminus.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Lys Lys Leu Leu Lys Lys Leu Lys Lys Leu
5 10
Leu Lys Lys Leu

(2) INFORMATION FOR SEQ ID NO:118:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

Leu Leu Lys Leu Leu Lys Lys Leu Leu Lys
5 10
Lys Leu Lys Lys

(2) INFORMATION FOR SEQ ID NO:119:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

Lys Leu Leu Lys Lys Leu Lys Lys Leu Leu
5 10
Lys Lys Leu Leu

(2) INFORMATION FOR SEQ ID NO:120:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Leu Leu Lys Lys Leu Lys Lys Leu Leu Lys
5 10
Lys Leu Leu Lys Leu Leu
15

(2) INFORMATION FOR SEQ ID NO:121:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:
Lys Lys Leu Leu Lys Lys Leu Leu Lys Lys
5 10
Leu Leu Lys Lys Leu
15

(2) INFORMATION FOR SEQ ID NO:122:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:
Gly Ile Gly Lys Phe Leu Lys Lys Ala Lys Lys
5 10
Phe Gly Lys Ala Phe Val Lys Ile Leu Lys Lys
15 20

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Gly Ile Gly Lys Phe Leu Lys Lys Ala Lys Lys
5 10
Phe Ala Lys Ala Phe Val Lys Ile Ile Asn
15 20
Asn

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa is ornithine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Leu Xaa Xaa Leu Leu Xaa Xaa Leu Xaa Xaa Leu
5 10

WHAT IS CLAIMED IS:

1. A compound, said compound being a conjugate of: (i) a biologically active amphiphilic peptide, said peptide being an ion channel-forming peptide, and said peptide being capable of forming an -helix; and (ii) a conjugate moiety selected from the group consisting of: (a) carbohydrates; (b) proteins; (c) polyvinyl pyrrolidone; (d) polyalkylene glycols; and (e) polyvinyl alcohol.

2. The compound of Claim 1 wherein said conjugate moiety is a carbohydrate.

3. The compound of Claim 2 wherein said carbohydrate is selected from the group consisting of dextran, hetastarch, hydroxyethyl starch, cellobiose, lactobiose, mannobiose, melibiose, lactobionic acid, and glucosamine.

4. The compound of Claim 3 wherein said carbohydrate is dextran.

5. The compound of Claim 3 wherein said carbohydrate is hetastarch.

6. The compound of Claim 1 wherein said conjugate moiety is a protein.

7. The compound of Claim 1 wherein said protein is selected from the group consisting of albumin and $_2$-macroglobulin.

8. The compound of Claim 1 wherein said conjugate moiety is polyvinyl pyrrolidone.

9. The compound of Claim 1 wherein said conjugate moiety is a polyalkylene glycol.

10. The compound of Claim 1 wherein said polyalkylene glycol is polyethylene glycol.

11. The compound of Claim 1 wherein said conjugate moiety is polyvinyl alcohol.

12. The compound of Claim 1 wherein said peptide is selected from the group consisting of:

(a) magainin peptides;

(b) PGLa peptides;

(c) XPF peptides;

(d) CPF peptides;

(e) cecropins;

(f) sarcotoxins;

(g) a peptide including one of the following basic structures X_{31} through X_{37}, wherein:

X_{31} is $-[R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}]_n-$;

X_{32} is $-[R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}]_n-$;

X_{33} is $-[R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}]_n-$;

X_{34} is $-[R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}]_n-$;

X_{35} is $-[R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}]_n-$;

X_{36} is $-[R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}]_n-$; and

X_{37} is $-[R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}]_n-$;

wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic, basic hydrophilic, or hydrophobic amino acid, and n is from 2 to 5;

(h) a peptide including the following basic structure X_{40}:

$R_{31}-R_{32}-R_{32}-R_{33}-R_{33}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{32}-R_{34}-R_{32}-R_{32}$, wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic or hydrophobic amino acid, and R_{34} is a basic hydrophilic or hydrophobic amino acid;

(i) a peptide including the following basic structure X_{50}:

$R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-$, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophobic amino acid;

(j) a peptide including the following basic structure X_{52}:

$R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-$, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid;

(k) a peptide including the following basic structure X_{54}:

$-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-$

R_{42}-R_{42}-R_{43}-, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid;

(l) a peptide including the following basic structure X_{56}:

-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{44}-, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{44} is a neutral hydrophilic amino acid or proline;

(m) a peptide including the following basic structure X_{58}:

-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{43}, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid;

(n) a peptide including the following basic structure X_{60}:

-R_{41}-R_{41}-R_{43}-R_{42}-R_{41}-R_{41}-R_{41}-R_{41}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{42}-R_{41}, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid;

(o) a peptide having a structure selected from the group consisting of:

(i) R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41};

(ii) R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41};

(iii) R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41};

(iv) R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}; and

(v) R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic amino acid or a neutral hydrophilic amino acid;

(p) a peptide, being in an amide- or carboxy-terminated form, said peptide being represented by the following structural formula, and the numbers below each amino acid residue refer to the position of the residue in the peptide:

LeuLysLeuLeuLysLysLeuLeuLysLysLeuLysLysLeuLeuLysLysLeu

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

or an analogue of said peptide wherein at least one of amino acid residues 1 through 7, 9, 11, 12, 14, 16, or 18 is deleted from said peptide;

(q) a peptide including the following structural formula X_{62}:

R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42} wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid;

(r) a peptide including the following structural formula X_{64}:

R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R41', wherein R_{41} is a hydrophobic amino acid and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

(s) a peptide including the following structural formula X_{66}:

R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}', wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

(t) a peptide including the following structural formula X_{68}:

R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42} -R_{42}-R_{41}, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid;

(u) melittin; and

(v) apidaecins.

13. The compound of Claim 12 wherein the peptide is a magainin peptide.

14. The compound of Claim 12 wherein the peptide is a PGLa peptide.

15. The compound of Claim 12 wherein the peptide is an XPF peptide.

16. The compound of Claim 12 wherein the peptide is a CPF peptide.

17. The compound of Claim 12 wherein the peptide is a cecropin.

18. The compound of Claim 12 wherein the peptide is a sarcotoxin.

19. The compound of Claim 12 wherein the peptide includes one of the following basic structures X_{31} through X_{37}, wherein:

X_{31} is $-[R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}]_n-$;

X_{32} is $-[R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}]_n-$;

X_{33} is $-[R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}]_n-$;

X_{34} is $-[R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}]_n-$;

X_{35} is $-[R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}]_n-$;

X_{36} is $-[R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}]_n-$; and

X_{37} is $-[R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}]_n-$, wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic, basic hydrophilic, or hydrophobic amino acid, and n is from 2 to 5.

20. The compound of Claim 12 wherein the peptide includes the following basic structure X_{40}:

$R_{31}-R_{32}-R_{32}-R_{33}-R_{34}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{32}-R_{34}-R_{32}-R_{32}$,

wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic or hydrophobic amino acid, and R_{34} is a basic hydrophilic or hydrophobic amino acid.

21. The compound of Claim 12 wherein said peptide includes the following basic structure X_{50}:

$R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}$,

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

22. The compound of Claim 12 wherein said peptide includes the following basic structure X_{52}:

$R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}$,

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

23. The compound of Claim 12 wherein the peptide includes the following basic structure X_{54}:
$-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{43}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid.

24. The compound of Claim 12 wherein the peptide includes the following basic structure X_{56}:
$-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{44}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{44} is a neutral hydrophilic amino acid or proline.

25. The compound of Claim 12 wherein the peptide includes the following basic structure X_{58}:
$-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{43}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid.

26. The compound of Claim 12 wherein the peptide includes the following basic structure X_{60}:
$-R_{41}-R_{41}-R_{43}-R_{42}-R_{41}-R_{41}-R_{41}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{42}-R_{41}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid.

27. The compound of Claim 12 wherein the peptide has a structure selected from the group consisting of:

(i) $R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(ii) $R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(iii) $R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(iv) $R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$; and

(v) $R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$,

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic amino acid or a neutral hydrophilic amino acid.

28. The compound of Claim 12 wherein said peptide is a peptide being in an amide- or carboxy-terminated form, said peptide being represented by the following structural formula, and the numbers below each amino acid residue refer to the position of the residue in the peptide:

Leu Lys Leu Leu Lys Lys Leu Leu Lys Lys Leu Lys
1 2 3 4 5 6 7 8 9 10 11 12
Lys Leu Leu Lys Lys Leu
13 14 15 16 17 18

or an analogue of said peptide wherein at least one of amino acid residues 1 through 7, 9, 11, 12, 14, 16, or 18 is deleted from said peptide.

29. The compound of Claim 12 wherein said peptide includes the following structural formula X_{62}:

R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42},

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

30. The compound of Claim 12 wherein said peptide includes the following structural formula X_{64}:

R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41},

wherein R_{41} is a hydrophobic amino acid and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

31. The compound of Claim 12 wherein said peptide includes the following structural formula X_{66}:

R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41},

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

32. The compound of Claim 12 wherein said peptide includes the following structural formula X_{68}:

R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42} -R_{42}-R_{41}, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

33. The compound of Claim 12 wherein said peptide is melittin.

34. The compound of Claim 12 wherein said peptide is an apidaecin.

35. A method of treating septic shock in a host, comprising: administering to a host a compound, said compound being a conjugate of: (i) a biologically active amphiphilic peptide, said peptide being an ion channel-forming peptide, and said peptide being capable of forming an -helix; and (ii) a conjugate moiety selected from the group consisting of: (a) carbohydrates; (b) proteins; (c) polyvinyl pyrrolidone; (d) polyalkylene glycols; and (e) polyvinyl alcohol, said compound being administered in an amount effective in treating septic shock in a host.

36. The method of Claim 35 wherein said conjugate moiety is a carbohydrate.

37. The method of Claim 36 wherein said carbohydrate is selected from the group consisting of dextran, hetastarch, hydroxyethyl starch, cellobiose, lactobiose, mannobiose, melibiose, lactobionic acid, and glucosamine.

38. The method of Claim 37 wherein said carbohydrate is dextran.

39. The method of Claim 37 wherein said carbohydrate is hetastarch.

40. The method of Claim 35 wherein said conjugate moiety is a protein.

41. The method of Claim 40 wherein said protein is selected from the group consisting of albumin and $_2$-macroglobulin.

42. The method of Claim 35 wherein said conjugate moiety is polyvinyl pyrrolidone.

43. The method of Claim 35 wherein said conjugate moiety is a polyalkylene glycol.

44. The method of Claim 43 wherein said conjugate moiety is polyethylene glycol.

45. The method of Claim 35 wherein said conjugate moiety is polyvinyl alcohol.

46. The method of Claim 35 wherein said peptide is selected from the group consisting of:

(a) magainin peptides;

(b) PGLa peptides;

(c) XPF peptides;

(d) CPF peptides;

(e) cecropins;

(f) sarcotoxins;

(g) a peptide including one of the following basic structures X_{31} through X_{37}, wherein:

X_{31} is $-[R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}]_n-$;

X_{32} is $-[R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}]_n-$;

X_{33} is $-[R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}]_n-$;

X_{34} is $-[R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}]_n-$;

X_{35} is $-[R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}]_n-$;

X_{36} is $-[R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}]_n-$; and

X_{37} is $-[R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}]_n-$;

wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic, basic hydrophilic, or hydrophobic amino acid, and n is from 2 to 5;

(h) a peptide including the following basic structure X_{40}:

$R_{31}-R_{32}-R_{32}-R_{33}-R_{33}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{32}-R_{34}-R_{32}-R_{32}$, wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic or hydrophobic amino acid, and R_{34} is a basic hydrophilic or hydrophobic amino acid;

(i) a peptide including the following basic structure X_{50}:

$R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-$, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophobic amino acid;

(j) a peptide including the following basic structure X_{52}:

$R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-$, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid;

(k) a peptide including the following basic structure X_{54}: $-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{43}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid;

(l) a peptide including the following basic structure X_{56}: $-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{44}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{44} is a neutral hydrophilic amino acid or proline;

(m) a peptide including the following basic structure X_{58}: $-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{43}$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid;

(n) a peptide including the following basic structure X_{60}: $-R_{41}-R_{41}-R_{43}-R_{42}-R_{41}-R_{41}-R_{41}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{42}-R_{41}$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid;

(o) a peptide having a structure selected from the group consisting of:

(i) $R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(ii) $R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(iii) $R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(iv) $R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$; and

(v) $R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic amino acid or a neutral hydrophilic amino acid;

(p) a peptide being in an amide- or carboxy-terminated form, said peptide being represented by the following structural formula, and the numbers below each amino acid residue refer to the position of the residue in the peptide:
LeuLysLeuLeuLysLysLeuLeuLysLysLeuLysLysLeuLeuLysLysLeu

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
or an analogue of said peptide wherein at least one of amino acid residues 1 through 7, 9, 11, 12, 14, 16, or 18 is deleted from said peptide;

(q) a peptide including the following structural formula X_{62}:

R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid;

(r) a peptide including the following structural formula X_{64}:

R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}, wherein R_{41} is a hydrophobic amino acid and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid;

(s) a peptide including the following structural formula X_{66}:

R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid;

(t) a peptide including the following structural formula X_{68}:

R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid;

(u) melittin; and

(v) apidaecins.

47. The method of Claim 46 wherein the peptide is a magainin peptide.

48. The method of Claim 46 wherein the peptide is a PGLa peptide.

49. The method of Claim 46 wherein the peptide is an XPF peptide.

50. The method of Claim 46 wherein the peptide is a CPF peptide.

51. The method of Claim 46 wherein the peptide is a cecropin.

52. The method of Claim 46 wherein the peptide is a sarcotoxin.

53. The method of Claim 46 wherein the peptide includes one of the following basic structures X_{31} through X_{37}, wherein:

X_{31} is $-[R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}]_n-$;

X_{32} is $-[R_{32}-R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}]_n-$;

X_{33} is $-[R_{32}-R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}]_n-$;

X_{34} is $-[R_{33}-R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}]_n-$;

X_{35} is $-[R_{31}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}]_n-$;

X_{36} is $-[R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}]_n-$; and

X_{37} is $-[R_{32}-R_{31}-R_{32}-R_{32}-R_{33}-R_{31}-R_{32}]_n-$, wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic, basic hydrophilic, or hydrophobic amino acid, and n is from 2 to 5.

54. The method of Claim 46 wherein the peptide includes the following basic structure X_{40}:

$R_{31}-R_{32}-R_{32}-R_{33}-R_{34}-R_{32}-R_{32}-R_{31}-R_{32}-R_{32}-R_{32}-R_{34}-R_{32}-R_{32}$,

wherein R_{31} is a basic hydrophilic amino acid, R_{32} is a hydrophobic amino acid, R_{33} is a neutral hydrophilic or hydrophobic amino acid, and R_{34} is a basic hydrophilic or hydrophobic amino acid.

55. The method of Claim 46 wherein said peptide includes the following basic structure X_{50}:

$R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}$,

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

56. The method of Claim 46 wherein said peptide includes the following basic structure X_{52}:

$R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}$,

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

57. The method of Claim 46 wherein the peptide includes the following basic structure X_{54}:
$-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{43}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid.

58. The method of Claim 46 wherein the peptide includes the following basic structure X_{56}:
$-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{44}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{44} is a neutral hydrophilic amino acid or proline.

59. The method of Claim 46 wherein the peptide includes the following basic structure X_{58}:
$-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{43}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid.

60. The method of Claim 46 wherein the peptide includes the following basic structure X_{60}:
$-R_{41}-R_{41}-R_{43}-R_{42}-R_{41}-R_{41}-R_{41}-R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-$
$-R_{41}-R_{42}-R_{42}-R_{42}-R_{41}-$, wherein R_{41} is a hydrophobic amino acid, R_{42} is a basic hydrophilic or neutral hydrophilic amino acid, and R_{43} is a neutral hydrophilic amino acid.

61. The method of Claim 46 wherein the peptide has a structure selected from the group consisting of:

(i) $R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(ii) $R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(iii) $R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$;

(iv) $R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$; and

(v) $R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}$,

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic amino acid or a neutral hydrophilic amino acid.

62. The method of Claim 46 wherein said peptide is a peptide, being in an amide- or carboxy-terminated form, said peptide being represented by the following structural formula, and the numbers below each amino acid residue refer to the position of the residue in the peptide:

Leu Lys Leu Leu Lys Lys Leu Leu Lys Lys Leu Lys
1 2 3 4 5 6 7 8 9 10 11 12
Lys Leu Leu Lys Lys Leu
13 14 15 16 17 18

or an analogue of said peptide wherein at least one of amino acid residues 1 through 7, 9, 11, 12, 14, 16, or 18 is deleted from said peptide.

63. The method of Claim 46 wherein said peptide includes the following structural formula X_{62}:

R_{41}-R_{41}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42},

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

64. The method of Claim 46 wherein said peptide includes the following structural formula X_{64}:

R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41},

wherein R_{41} is a hydrophobic amino acid and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

65. The method of Claim 46 wherein said peptide includes the following structural formula X_{66}:

R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41},

wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

66. The method of Claim 46 wherein said peptide includes the following structural formula X_{68}:

R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}-R_{42}-R_{41}-R_{41}-R_{42}
-R_{42}-R_{41}, wherein R_{41} is a hydrophobic amino acid, and R_{42} is a basic hydrophilic or neutral hydrophilic amino acid.

67. The method of Claim 46 wherein said peptide is melittin.

68. The method of Claim 46 wherein said peptide is an apidaecin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11841

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07K 7/04, 9/00; A61K 37/02
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/322, 324, 326, 327, 328, 345; 514/008, 012, 013, 014, 015; 525/541

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, MEDLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US, 5,208,220 (BERKOWITZ) 04 May 1993, see entire document.	1-68
A,P	US, 5,217,956 (ZASLOFF et al.) 08 June 1993, see entire document.	1-68
A,P	US, 5,221,664 (BERKOWITZ et al.) 22 June 1993, see entire document.	1-68

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 08 March 1994	Date of mailing of the international search report 16 MAR 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer CAROL A. SALATA Jill Warden for Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11841

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

530/322, 324, 326, 327, 328, 345; 514/008, 012, 013, 014, 015; 525/541